The Journal of Pediatrics

VOL. 45 JULY, 1954 NO. 1

THE TREATMENT OF NUTRITIONAL ANEMIA IN INFANCY AND CHILDHOOD WITH ORAL IRON AND ASCORBIC ACID

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THE basic etiological factor in hypochromic anemias is the depletion or inadequacy of the body's iron stores. Iron deficiency anemia develops in a large number of young children.[1, 2] An infant's normal iron balance may be deranged by excessive demand for iron due to rapid growth,[3, 4] iron-deficient diet,[2, 5] defective iron absorption,[6] deficient iron storage (faulty prenatal maternal diet, prematurity, twin birth, early clamping of umbilical cord),[3, 7, 8, 9] infections,[3] hypochlorhydria,[3, 10] and gastrointestinal disorders (intestinal polyps, colitis, or celiac disease).[11] Nutritional anemia is more common in children between the ages of 6 to 36 months than at any other age as they are particularly vulnerable to the mentioned factors.[1, 2]

When iron deficiency anemia occurs, several diagnostic features manifest themselves in the history and physical examination, and a typical blood picture is encountered. Active and normal erythropoiesis reappears and is accompanied by a short period of reticulocytosis after the administration of iron. The hemoglobin level increases, and symptomatic improvement occurs rapidly. The appetite becomes normal; strength is regained; physical findings disappear.[12]

The absorption of iron takes place chiefly in the duodenal region. This and other mechanisms of iron metabolism have been investigated.[13, 14, 15] It has been demonstrated that iron absorption is decreased significantly by milk or a high phosphate content in food,[6, 16, 17] phytates in oatmeal and brown bread,[6, 16] alkaline foods and medications,[18] an excess of calcium,[19] and to a minor degree achlorhydria.[12] The logical time for the administration of therapeutic oral iron preparations in infants and children would seem to be at a time when little or no food is present in the stomach. Iron is most efficiently absorbed in the ferrous state and adequate conversion of ferric iron in foods to ferrous iron is of definite advantage. This conversion is aided by the presence of ascorbic acid, cysteine- and sulfhydryl-containing compounds, and by the gastric hydrochloric acid in the stomach.[21, 22] Moore and Dubach[20] studied the effect of ascorbic acid on the amount of iron absorbed by the body, and concluded that the presence of as-

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corbic acid increases iron absorption, regardless of body iron supply, hemoglobin level, or achlorhydria.

The dietary substances thought to be important for erythrocyte production and hemoglobin formation are iron, certain amino acids (methionine, tryptophane, isoleucine), and the vitamins folic acid, vitamin B_{12}, and ascorbic acid.[22] Deficiency of these substances can result from an inadequate diet or from ineffective utilization.

It is the purpose of this study to show that ascorbic acid and oral iron is a more effective mode of therapy in the treatment of nutritional anemia of infants and children than oral iron alone.

MATERIALS AND METHODS

This study is founded on the observations of twenty infants and young children diagnosed as having nutritional (iron deficiency) anemia. Other causes of anemia were ruled out. The presence of nutritional anemia and a hemoglobin of 7 Gm. or less per 100 c.c. of whole blood were the only requirements. The latter was felt necessary to obtain a homogeneous group of moderate to severe cases of anemia. Such a group was chosen to avoid certain variables encountered with milder cases, to obtain less of a spread in hemoglobin levels, and to be able to reach more valid conclusions in regard to response to therapy. The patients in this study represent a random group of patients seen and diagnosed on the wards and in the outpatient service of the Pediatric Department, University of Maryland Hospital, during the period from June, 1952, to June, 1953.

The patients were divided into two groups by the alternating case method. Group 1 was treated by an oral iron preparation* and a standard vitamin supplement.† Group 2 was treated identically to Group 1, *except that each patient in Group 2 received ascorbic acid in addition.* The total daily vitamin C dose of 500 to 750 mg. was divided into three equal doses given about one-half hour before meals. The vitamin supplement was received once daily by all patients in the amount of 0.6 c.c. The dosage of the iron preparation was adjusted for each patient to receive between 20 and 25 mg. of elemental iron per kilogram per day. This was administered in three to four divided doses between meals. No untoward symptoms, such as gastrointestinal irritation, constipation or diarrhea, nor any toxic manifestations were observed.

The hemoglobin levels were measured in a Klett-Summerson photoelectric colorimeter. Reticulocytes were enumerated in smears stained vitally with brilliant cresyl blue. Sickling tests were done by the sodium bisulfite method.[23] The blood indices (Wintrobe constants) were determined by the method described by Wintrobe.[12] Iron utilization figures were obtained by the method of Heath and Patek.[4]

The method of hematologic study was identical in all patients observed. The initial examination of the peripheral blood consisted of a blood smear, hemoglobin level, hematocrit, eryth-

*Rubraton Elixir, Squibb. Each 5 c.c. supplies ferric ammonium citrate U.S.P. 220 mg. providing 38 mg. of elemental iron; folic acid 0.28 mg.; and vitamin B_{12} 4.17 μg. This product contains 12 per cent alcohol by volume, is buffered to an acid pH, and contains no phosphates.

†Poly-Vi-Sol, Mead Johnson.

rocyte count, total and differential leukocyte count, reticulocyte count, and a sickling test on all Negroes. Hemoglobin levels and reticulocyte counts were determined every three to four days for the first two weeks. Thereafter, they were obtained every five to seven days for as long as the patient would keep the clinic appointments. At the termination of the treatment period, or a few days later, a complete blood study was done identical to the initial examination. Wintrobe constants were calculated from the two complete blood studies.

A statistical evaluation was done in the following way. The average daily hemoglobin response for the first fifteen days after onset of treatment was determined for each patient in the two groups (hemoglobin in grams per 100 c.c. on the fifteenth day minus initial hemoglobin in grams per 100 c.c.; the result was divided by 15). The mean average daily hemoglobin response was then calculated for each group, and the difference of the two means found. Second, the reticulocyte response of each patient in the two groups was derived (peak reticulocytosis in percentage minus initial reticulocyte count in percentage). Again the mean for each group was found and the difference of the two means determined. The standard deviation, the correction of same, the standard error, and the standard error of difference between two means were all calculated according to the formulas and procedure as outlined by Bradford-Hill.[25]

About one-third of all patients were followed in the outpatient department w i t h o u t hospitalization. The others were observed first in the hospital, usually for short periods. Attempts at dietary regulation were not necessary as the children voluntarily started to take an adequate diet within a few days after treatment was begun. The patients in this study ranged in age from 8 to 29 months. There were eleven males and nine females. In Group 1, the mean age was 14.4 months, with a range of 8 to 29 months. In Group 2, the mean age was 18.5 months, with a range of 9 to 24 months.

OBSERVATIONS AND RESULTS

1. *Analysis of clinical history and objective findings* at time of admission of all patients was as follows:

Dietary history: Fourteen of the patients had received a milk diet exclusively, while six were taking a diet lacking meats and vegetables.

Incidence of prematurity and twin birth: Present in seven cases.

Previous illnesses and other conditions: A history of upper respiratory infections was elicited with consistency and manifested by sixteen of the patients.

Observations made by mother pertaining to the anemia: Anorexia, inactivity, easy fatigability, lethargy, poor weight gain or loss of weight, irritability, and slow development were common complaints (listed in order of decreasing frequency).

Observations on initial physcial examination: Marked pallor of the skin, mucous membranes, and nail beds was observed in all patients. Fifteen children displayed undernutrition or malnutrition, usually minimal. Some developmental retardation was demonstrated in sixteen cases. This was primarily motor, but skeletal and mental retardation was

present also in a few patients. Hepatosplenomegaly and hemic murmurs were found in seventeen of the children. Fourteen of the patients had an upper respiratory infection on admission, sometimes associated with a temperature of over 102° F. Other diseases were observed at times, such as diarrhea, vomiting, bronchitis, scabies, cystitis, and rickets. Altogether, eighteen of the patients had some infection at the time of admission.

2. *Comparison of Group 1* (oral iron) *and Group 2* (oral iron and ascorbic acid) on the basis of mean initial hemoglobin, average daily hemoglobin response, mean peak reticulocytosis with mean day of occurrence, average length of treatment and mean number of days until a normal hemoglobin level was attained (see Table I).

3. *Hemoglobin levels* (see Fig. 1):

Initial hemoglobin: The average for Group 1 was 5.1 Gm. per 100 c.c., the range being 4.2 to 7.0 Gm. per 100 c.c. The average for Group 2 was 4.2 Gm. per 100 c.c., the range being 2.8 to 5.3 Gm. per 100 c.c. It might be stated that 85 per cent of all patients studied fell within the initial hemoglobin range of 3.1 to 5.6 Gm. per 100 c.c.

Hemoglobin levels during the treatment period: Within nine days, the average hemoglobin for Group 1 was 7.1 Gm., and for Group 2, 8.1 Gm. After 15 days, the average hemoglobin for Group 1 was 8.7 Gm., and for Group 2, 10.0 Gm. At the 20-day mark, the average hemoglobin for Group 1 was 9.7 Gm., and for Group 2, 10.8 Gm. per 100 c.c.

TABLE I

GROUP	MEAN INITIAL Hg.	AVERAGE DAILY Hg. RESPONSE	MEAN PEAK RETICULOCYTOSIS	MEAN DAY OF OCCURRENCE	AV. LENGTH OF TREATMENT	TIME REQUIRED TO REACH A Hg. OF 11 GM.
1.	5.1 Gm. per 100 c.c.	0.205 Gm.	13.6%	9.0 da.	21 da.	29 da.
2.	4.2 Gm. per 100 c.c.	0.347 Gm.	26.7%	9.6 da.	17 da.	21 da.

It may be noted from Table I that Group 2 had an average daily hemoglobin response of 69 per cent greater than Group 1. The average peak reticulocytosis was 96 per cent higher in Group 2 as compared with Group 1, but the day of occurrence was about the same. The average length of treatment was shortened by 19 per cent in Group 2, but the average day of an adequate hemoglobin response occurred eight days, or 28 per cent, sooner in the patients of Group 2.

Maximal hemoglobin response: The average for Group 1 resulted in 11.0 Gm. per 100 c.c., with a range of 10.0 to 11.6 Gm. This was reached at a mean of 29 days after initiation of treatment. The average maximal hemoglobin for Group 2, however, reached 11.7 Gm. per 100 c.c., with a range of 11.0 to 12.5 Gm. This level was attained at a mean of 30 days. After the first 30 days beyond the start of therapy, hemoglobin levels for both groups fluctuated between 10.6 and 12.5 Gm. per 100 c.c. for

those patients who were followed as long as two months. The children of Group 2 had the tendency to have hemoglobin levels consistently higher than those of Group 1.

Average daily hemoglobin response: Group 1 had a mean of 0.205 Gm. per day and a range of 0.159 to 0.256 Gm. per day. Results in Group 2 reached a mean of 0.347 Gm. per day, with a range of 0.310 to 0.436 Gm. per day. (See Fig. 2.)

Statistical analysis: The average daily hemoglobin rise during the first 15 days of treatment is shown in Table II. The standard error of difference between the two means equals 0.021 Gm. per 100 c.c. The difference in the two means is 0.161 Gm. per 100 c.c. It is thereby shown that the difference in the two means exceeds the standard error of means by 7.7 times ($0.161 \div 0.021$), or almost four times more than required to be significant.

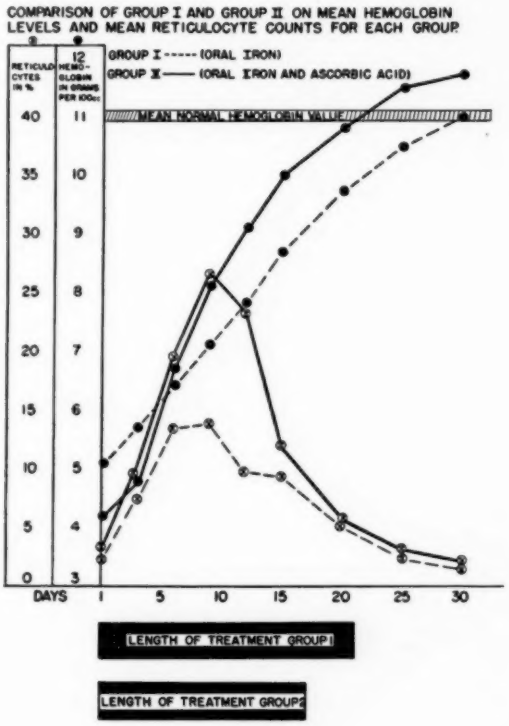

Fig. 1.

4. *Erythrocytes:* An erythropenia was observed initially in 55 per cent of the cases. Counts within the normal range occurred in the remainder, being fairly evenly divided between the two groups. The counts in both groups were all in the normal range after therapy.

5. *Reticulocytes* (see Fig. 1): The initial reticulocyte counts of all patients were within the normal range

or slightly elevated, the mean being 2.95 per cent. All patients showed a reticulocyte response within two to three days after the start of either treatment regimen. A peak reticulocytosis was reached by the sixth to the twelfth day, the average being 9 days for Group 1 and 9.6 days for being a mean of 13.6 per cent for Group 1 and a mean of 26.7 per cent for Group 2. The ranges were 9.2 to 19.1 per cent and 18.2 to 39.8 per cent, respectively (see Fig. 2).

Statistical analysis of the reticulocyte count increase is given in Table III. The standard error of difference

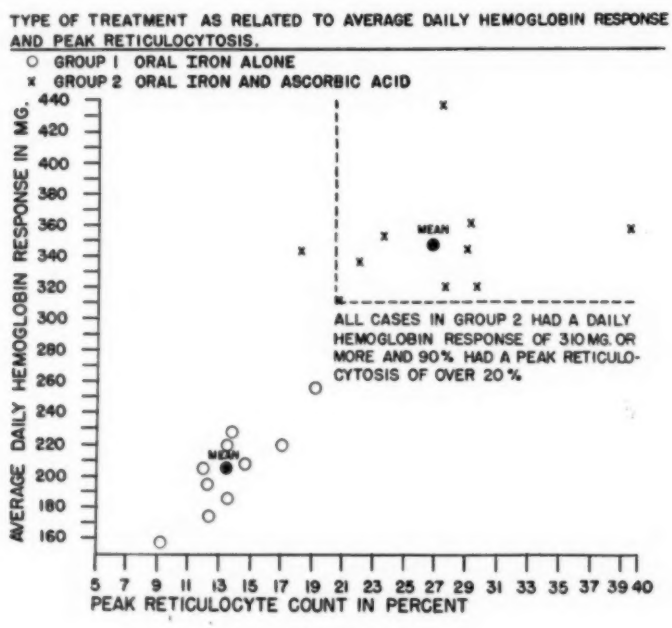
TYPE OF TREATMENT AS RELATED TO AVERAGE DAILY HEMOGLOBIN RESPONSE AND PEAK RETICULOCYTOSIS.
○ GROUP 1 ORAL IRON ALONE
× GROUP 2 ORAL IRON AND ASCORBIC ACID
AVERAGE DAILY HEMOGLOBIN RESPONSE IN MG.
440
420
400
380
360
340
320
300
280
260
240
220
200
180
160
MEAN
MEAN
ALL CASES IN GROUP 2 HAD A DAILY HEMOGLOBIN RESPONSE OF 310 MG. OR MORE AND 90% HAD A PEAK RETICULOCYTOSIS OF OVER 20%
5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 40
PEAK RETICULOCYTE COUNT IN PERCENT

Fig. 2.

TABLE II

	GROUP 1	GROUP 2
Mean average daily hemoglobin rise	0.222 Gm./100 c.c.	0.383 Gm./100 c.c.
Standard deviation (corrected)	0.055 Gm./100 c.c.	0.040 Gm./100 c.c.
Standard error	0.018 Gm./100 c.c.	0.013 Gm./100 c.c.

Group 2. The reticulocytes gradually decreased thereafter and often reached normal levels after the twenty-first to the twenty-fifth day. The difference between the two groups manifested itself in the degree of the peak reticulocytosis, this between the two means equals 2.03 per cent. The difference between the two means is 12.6 per cent and is 6.2 times greater than the standard error of difference between the two means. The degree of difference allowable by chance is twice the standard error

of means. The result of 6.2 is obviously statistically significant.

6. *Wintrobe indices:* It may be observed from Table IV that the MCVs approximated the normal range following therapy. The MCH and MCHC responses are more delayed, and, except for a few, have not quite reached the normal range at this time. There is little difference between the two groups in regard to the three indices.

7. *Weight gain:* The average weight gain of all patients was 0.895 kilograms during the course of therapy.

8. *General observations:* All patients showed marked improvement in physical condition with disappearance of pallor during the course of treatment. The children became active, cheerful, sociable, and playful. A voluntary dietary adjustment took place within a few days after the onset of therapy. On the average, this occurred on the seventh day for Group 1 and on the fourth day for Group 2. The patients decreased their milk intake and developed a liking for foods such as meats, fruits, vegetables, and eggs. The visceromegaly disappeared within twelve to fifteen days, but it took longer for the hemic murmur to subside, commonly four weeks or more.

Fig. 3 (Group 1) and Fig. 4 (Group 2) represent an average case of each group.

DISCUSSION

The oral use of iron in nutritional anemia has been well established. However, the proper dosage of iron, the type of preparation, and the supportive therapy must be chosen carefully. Iron and ammonium citrate was used in this study because the ferrous salts, while perhaps absorbed more efficiently, are difficult to give in simple watery solutions as oxidation will produce the ferric form.[12] The administration of iron in an acid-buffered medium produces a greater reticulocyte response, indicating better absorption.[26] Both ferrous and ferric salts will produce a satisfactory hemoglobin response when proper doses are used, and care in technical details of administration is exercised. Failure to respond to oral iron is rare in nutritional anemia of infancy and childhood.[27]

TABLE III

	GROUP 1	GROUP 2
Mean reticulocyte count increase	11.0%	23.6%
Standard deviation (corrected)	2.6%	5.9%
Standard error	0.8%	1.8%

TABLE IV

		GROUP 1		GROUP 2	
		PRE-THERAPY	POST-THERAPY	PRE-THERAPY	POST-THERAPY
Mean corpuscular volume in cubic microns	Average	55	72	51	73
	Range	51-63	65-78	41-62	65-76
Mean corpuscular hemoglobin in micromicrograms	Average	13	21	13	21
	Range	11-15	19-24	10-15	18-23
Mean corpuscular hemoglobin concentration in percentage	Average	24	29	25	29
	Range	20-25	26-30	23-27	28-30

The mechanisms by which certain factors such as folic acid, vitamin B_{12}, and ascorbic acid influence erythrocyte formation, hemoglobinization, and maturation are still not entirely clarified. However, they do seem to play a part in the synthesis of nucleic acids.[28] It may be that other factors besides iron could be deficient in nutritional anemia. By the addition of some of the above-mentioned factors to the treatment regimen, the period of recovery may be shortened through their effect on nucleic acid synthesis and the consequent production of normal erythrocytes. The effect of folic acid and vitamin B_{12} when given with iron in nutritional anemia seems to be negligible. It might be postulated, however, that ascorbic acid not only increases iron absorption, but also improves the utilization of iron.

The children in this study suffered from severe nutritional anemia. Some patients were quite ill with an infection on admission, but their response to therapy seemed equal to the response of those without an infection. Several patients contracted an infection while under observation, but this did not materially affect their hemoglobin response. It should be emphasized that seriously ill and anemic children should receive a blood transfusion. No other mode of antianemic therapy should be relied on. Oral iron can and should be pre-

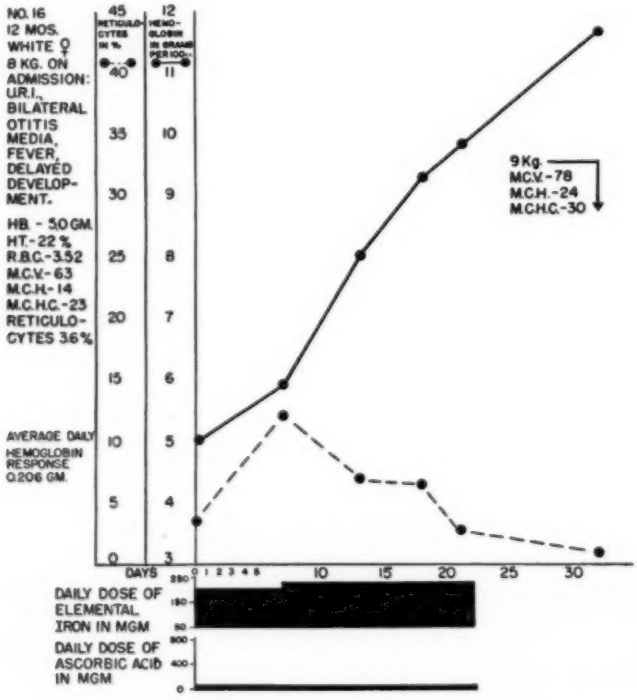

Fig. 3.

scribed after the emergency has subsided because a blood transfusion will not appreciably influence the nutritional deficiency which is invariably present. In all other cases of nutritional anemia, even if the anemia is severe and a mild to moderate infection is present, transfusions should be avoided. The danger of transfusion reactions is increased in the more anemic patients.[29]

ness of this iron preparation.[31] This mode of therapy is best reserved for those rare occasions when oral iron cannot be tolerated or the nutritional anemia is "refractory" to oral iron[5, 27]

It seems that most children with iron deficiency anemia respond equally well to either oral or intravenous iron. This is demonstrated when one compares the mean daily

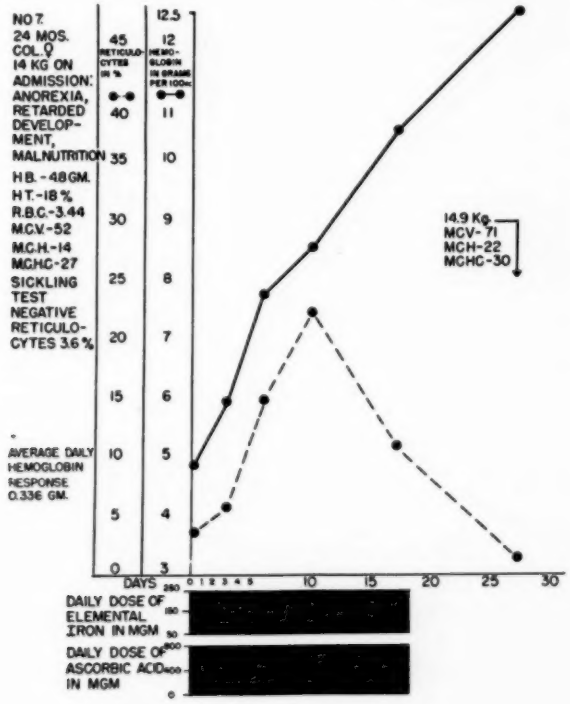

Fig. 4.

The intravenous injection of a saccharated oxide of iron is efficient in hypochromic anemias.[30] The narrow margin of safety with the amount injected, the occurrence of untoward reactions, and the necessity of an intravenous injection with possible technical difficulties limit the usefulhemoglobin response, reticulocytosis, and time of adequate response between Group 1 of this study and the results reported by Dickstein and associates.[30] In contrast, it may be observed from the responses of the children in Group 2 that ascorbic acid exerts a favorable effect when given

with oral iron. The mean daily hemoglobin response in this group was 69 per cent greater, the peak reticulocytosis 96 per cent higher, and the calculated iron utilization percentages 55 per cent more than in Group 1 (see Fig. 5). Indirectly, the degree of reticulocytosis reflects on the efficiency of iron utilization. Statistical evaluation of the hemoglobin response and the reticulocytosis shows that the differences are significant. Therefore, it is felt that ascorbic acid does aid in the absorption and possibly the utilization of iron in a nutritional anemia of infancy and childhood.

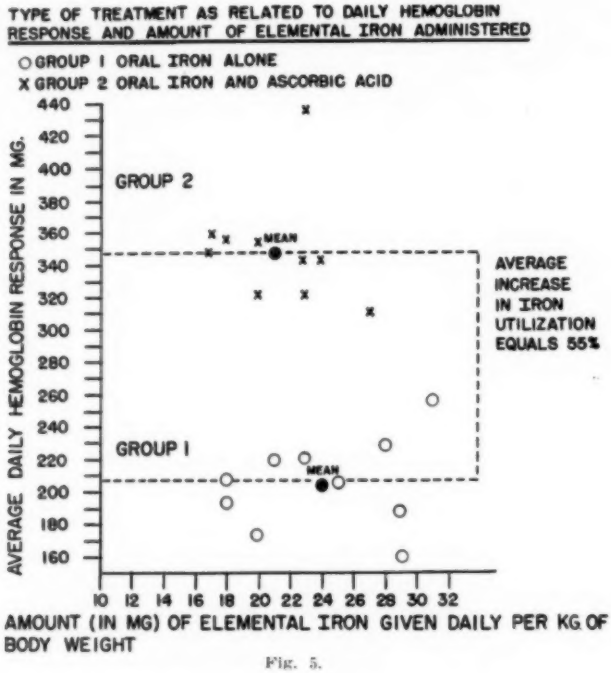

Fig. 5.

It was concluded that a fourteen- to seventeen-day course of therapy is adequate. The oral iron should be administered in the amount of 20 mg. of elemental iron per kilogram of body weight per day. The ascorbic acid should be prescribed in the amount of 500 to 800 mg. daily. This regimen will produce a good recovery from nutritional anemia. It will adequately replenish the patient's iron stores and will result in the child's taking a balanced diet voluntarily in most instances.

SUMMARY

The subject of nutritional anemia in infancy and childhood is reviewed, with emphasis on the etiology, the pathogenesis, and the mechanisms of iron metabolism involved.

In twenty infants and children with severe nutritional anemia, satisfactory therapeutic results were obtained when oral iron was administered. Every other patient in this

series received large doses of ascorbic acid additionally which improved the response to iron therapy.

The observations were critically analyzed and evaluated. The hemoglobin values were restored rapidly to a normal range in all cases. The average daily hemoglobin response in the group treated with oral iron alone was 0.205 Gm. The average daily hemoglobin response in the group treated with oral iron and ascorbic acid amounted to 0.347 Gm. The average length of treatment in the first group was twenty-one days, while the same was achieved after seventeen days of therapy in the second group.

It is concluded that the oral administration of iron in nutritional anemia of infancy and childhood is equally efficacious as other types of treatment. Apparently ascorbic acid increases the absorption and to some extent may aid the utilization of orally given iron.

We wish to express our appreciation to Miss Lenore A. Schwartz, A.B., for her technical assistance, and to the members of the pediatric house staff for their interest and cooperation in this work.

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HYDROCARBON PNEUMONITIS FOLLOWING FURNITURE POLISH INGESTION

A Report of Fifteen Cases

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THE ingestion of hydrocarbons, e.g., kerosene, gasoline, lighter fluid, or furniture polish, is a common pediatric emergency. Since the ingestion of such materials may have delayed or serious effects, many hospitals have established a policy of admitting all patients with a history of hydrocarbon ingestion for a two-to three-day period of observation regardless of the presenting symptomatology. This policy has been in effect for the past four years at Jefferson Davis City-County Hospital where approximately 100 such patients are admitted yearly. One group, i.e., those patients ingesting red furniture polish, have consistently had a more severe clinical course and a considerably longer period of hospitalization.

In the medical literature, only three references to red furniture polish ingestion were found. Sullivan[1] described a severely ill patient who was admitted to the hospital thirty hours following the ingestion of approximately one ounce of "Old English" red furniture polish. This patient remained critically ill and febrile for eight days with a severe and slowly resolving pneumonitis. Hoffmann and Bell[2] described the clinical findings and course in an infant who ingested approximately 120 c.c. of red furniture polish. This child rapidly developed a severe pneumonitis and was critically ill for nineteen days. Heacock,[3] in a review of hydrocarbon pneumonitis in children, mentions two cases of pneumonitis following furniture polish ingestion. He felt that both of these demonstrated some of the radiologic features of a lipoid pneumonia and noted that resolution was much slower than is usually seen in pneumonitis associated with kerosene ingestion.

The red furniture polish ingested by our patients is marketed under the following trade names: "Holder's Supreme Wax Oil Polish," "Old English Red Furniture Polish," "O'Cedar All Purpose Polish (Red)," and "Shur Shine." A basic constituent of each of these products is mineral seal oil, which may constitute from 20 to 99 per cent of the volume of the finished product. "Old English" and "O'Cedar" are 99 per cent mineral seal oil. The Holder's product contains only 10 to 20 per cent mineral seal oil; the remaining portion is largely kerosene. To this hydrocarbon base, less than 1 per cent by volume of various odorizing and coloring agents is added. These include oil of cedarwood, methyl salicylate, turpentine, oil of camphor, oil of cedarleaf, lemon oil, and traces of aniline dye for coloring purposes. Mineral seal oil is a light petroleum oil obtained as a fraction

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TABLE I. PERTINENT FINDINGS IN SEVENTEEN CHILDREN WHO DEVELOPED PNEUMONITIS FOLLOWING THE INGESTION OF RED FURNITURE POLISH

PATIENT	AGE, RACE, SEX	AMT. TAKEN (OZ.)	PRODUCT	GAG AND/OR COUGH	VOMIT AND/OR LAVAGE	FIRST SIGN OR SYMPTOM	TIME FROM INGESTION TO ELEV. OF TEMP.	MAX. TEMP.	INITIAL WBC AND % POLYS	DAYS FEBRILE	PNEUMONITIS BY X-RAY	COMMENTS
1. L. K.	14 mo. Negro Male	½-1	Unknown	+	0	Lethargy	12 hr.	102°	14,900 46% P.	3	+	
2. B. J. H.	18 mo. Negro Female	½-1	Unknown	+	+	Semicoma	18 hr.	101.4°	15,500 70% P.	2	+	
3. B. G. B.	16 mo. Negro Female	?	Unknown	0	+	Lethargy	2 hr.	103.8°	16,900 69% P.	15	+	Convalescing from measles at time of ingestion
4. L. C.	20 mo. Negro Male	1-2	Old English	0	+	Fever and dyspnea	5 hr.	105°	6,000 58% P.	10	+	
5. G. R.	14 mo. Negro Male	?	Old English	+	0	Cough and fever	48 hr.	105.4°	11,200 70% P.	3	+	Furniture polish in dark liquid stools 24 hr. after ingestion. Asymptomatic for 48 hr.
6. C. S.	16 mo. Negro Male	?	Old English	+	Induced vomiting	Lethargy	18 hr.	104.2°	33,900 80% P.	–	+	Died in coma on sixth hospital day
7. C. G.	24 mo. White Female	?	Holder's	+	+	Semicoma	3 hr.	102.4°	17,600 74% P.	2	+	
8. C. McC.	11 mo. Negro Male	1	Holder's	+	0	Coma	5 hr.	103.4°	8,300 % P. ?	2	+	

9. B. L. J.	12 mo. Negro Female	3-4	O'Cedar	+	Induced vomiting	Lethargy and fever	18 hr.	103.4°	11,000 54% P.	–	+	Died in coma on third hospital day
10. D. B. D.	15 mo. White Male	?	O'Cedar	0	+	Lethargy and pallor	?	104°	19,100 72% P.	13	+	Severely ill for 13 days
11. M. W.	24 mo. White Male	2-3	Old English	+	+	Lethargy and pallor	2 hr.	105.6°	35,900 92% P.	14	+	Initially afebrile in 48 hours. Left hospital against medical advice and returned at 72 hr. in critical state
12. D. L. C.	20 mo. White Male	3-4	Shur Shine	?	+	Semicoma	2 hr.	105°	13,100 69% P.	10	+	Critical condition for 1 week
13. G. A.	20 mo. Negro Male	½	Holder's	0	+ 2 hr. after ingestion	Lethargy	2½ hr.	103.4°	?	1	+	
14. S. L. Mc.	13 mo. Negro Male	?	O'Cedar	+	0	Lethargy	No fever	No fever	12,000 58% P.	0	+	X-ray evidence of pneumonitis on admission. Began clearing at 48 hr.
15. M. A. E.	13 mo. White Female	½	Old English	+	0	Wheezing and respiratory difficulties	?	104°	27,790 53% P.	6	+	First seen 18 hr. after ingestion
16. D. T.	15 mo. Negro Female	1	Old English	?	0	Lethargy	24 hr.	103.8°	8,700 59% P.	8	+	Reference 2
17.	12 mo. White Female	4	?	+	+	Pallor and dyspnea	?	?	?	19	+	Reference 1

of distillate from crude petroleum in the range of 500 to 700° F. The relative composition of a particular mineral seal oil will vary with the source of the crude petroleum. This refined petroleum hydrocarbon contains unsaturated and saturated aliphatic and aromatic hydrocarbons. The unsaturated aliphatic hydrocarbons are largely removed by acid washings. The resulting product is composed principally of saturated aliphatic hydrocarbons of a higher molecular weight than those characteristic of gasoline or kerosene. It also contains some cyclic and branched chain compounds. This product should not be confused with mineral oil (liquid petrolatum, U.S.P.) which is a highly refined oil of high molecular weight composed principally of saturated aliphatic petroleum hydrocarbons.

The present report is concerned with an evaluation of the clinical findings and course of fifteen children who were hospitalized following the ingestion of red furniture polish.

Table I shows the pertinent findings in the fifteen patients. The majority show symptoms and signs of (a) intoxication, and (b) pneumonitis. The two cases reported in detail in the literature[1, 2] are included as Nos. 16 and 17. Cases 2, 5, 6, 9, and 12 are given in short individual case reports.

CASE REPORTS

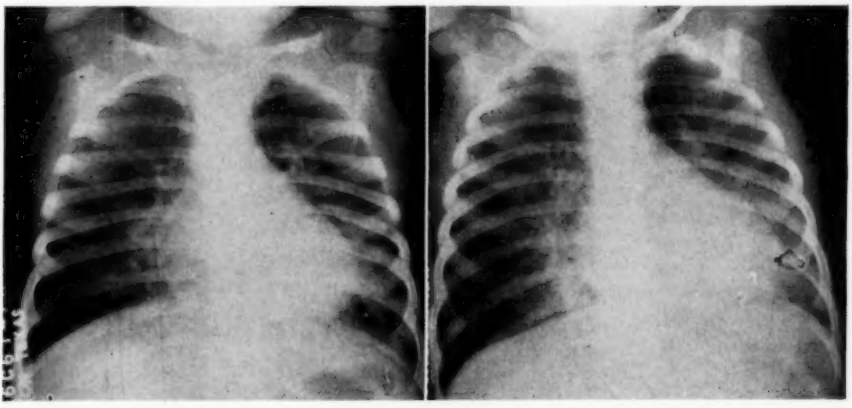
CASE 2.—B. J. H., an 18-month-old Negro female, arrived at the hospital approximately thirty minutes after the parents had seen her drink one-half to one ounce of red furniture polish. The parents reported that the child "gagged" immediately, coughed and appeared to "strangle." In the emergency room, gastric lavage was performed and the patient was admitted to the hospital. On admission, she was cyanotic, flaccid, unresponsive, and semicomatose. The patient was placed in an oxygen tent and given stimulants with subsequent improvement in her condition. Physical examination revealed pulse 120, blood pressure 100/64, and temperature 98° F. There was marked flaring of the alae nasae and an expiratory grunt. The chest was clear to auscultation and percussion. Neurological examination revealed only marked lethargy. White blood cell count was 15,500 with 70 per cent polymorphonuclears and 30 per cent lymphocytes. Hemoglobin was 10.9 Gm. per cent; red blood count was 5.24 million. Urinalysis was essentially negative. Admission chest radiograph was normal.

In the hospital, her temperature rose rapidly to 101.4° F. in spite of intramuscular penicillin and streptomycin therapy. This temperature elevation subsided by the end of the second hospital day. Repetition of the chest radiograph at this time revealed an infiltration in the medial third of both lung fields. A film taken four days later showed complete clearing of this process. The patient was discharged on the eleventh hospital day. A clinic visit one week later revealed only a minimal residual cough and no abnormal physical findings.

This patient is typical of the milder course exhibited by children who have ingested only a small quantity of furniture polish. Although the quantity taken was not great, the immediate treatment at home and in the emergency room of the hospital gave ample opportunity for aspiration. Her rapid recovery may possibly be ascribed to prompt administration of prophylactic antibiotics.

CASE 5.—G. R., a 14-month-old Negro male infant, consumed an unknown quantity of "Old English" red furniture polish. He coughed im-

mediately, was given a glass of milk which he took without difficulty, and returned to play in an apparently normal condition. The following morning (sixteen hours later) the patient passed three dark, liquid stools with a "strong odor of furniture polish." He was otherwise asymptomatic until the afternoon of the second day (forty hours after ingestion of the red furniture polish), when he developed a cough, fever, and was noted to have rapid, shallow, grunting respirations. At this time, he was brought to the hospital emergency room and immediately admitted to the wards.



A. *B.*

Fig. 1.—D. L. C. *A*, First examination sixteen hours after ingestion shows emphysema particularly involving right lower lung field. *B*, On the fourth hospital day, the punctate appearance of the peribronchial infiltration and the preservation of peripheral aeration are shown.

Examination revealed a lethargic, febrile, acutely ill child lying quietly in bed. Respiration was 90, pulse 160, temperature 105° F. Skin was hot and dry. Râles and bronchial breathing were noted over the right base posteriorly. He was placed in an oxygen tent and started on antibiotic therapy, but temperature of 104° F. continued for the next two days. Thereafter he remained afebrile. Admission chest radiograph was negative, but one taken two days after admission revealed bilateral central pneumonia. Although the patient was well clinically, roentgen findings were still present thirteen days after the onset of clinical signs and symptoms. Admission hemoglobin was 10.9 Gm. per cent, white blood cell count was 11,200 with 70 per cent polymorphonuclears. Urinalysis was negative.

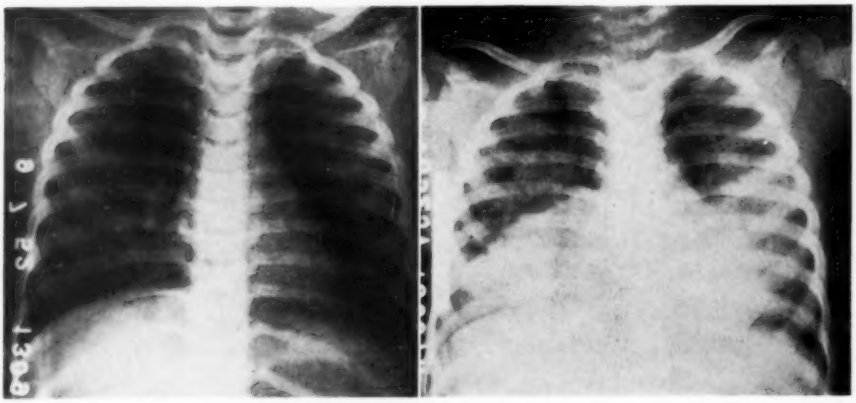
The lapse of some forty hours between the time of red furniture polish ingestion by this infant and the onset of symptomatology is unique in this series. The diarrheal stools passed the day after ingestion suggest that the patient had taken a generous quantity. The cough was not emphasized in the history and other evidence of aspiration is lacking. It is therefore possible that this patient's findings may represent an example of so-called "excretory pneumonitis."

Case 12.—D. L. C., a white male infant, was admitted to the hospital with the history of drinking about one cup of "Shur-Shine" red furniture polish two hours prior to admission. Thirty minutes later, during gastric lavage, the patient vomited twice and had two loose stools.

Shortly thereafter, he became listless and semicomatose. On admission, his temperature was 101° F., respiration 30, and pulse 130. The respirations were labored and grunting. The abdomen was distended. No râles were heard over the chest. The hemoglobin was 9.6 Gm. per cent and red blood cell count was 3.52 million. White blood cell count was 10,100 with 62 per cent polymorphonuclears and 38 per cent lymphocytes. Urinalysis was negative except for a trace of albumin. A chest radiograph (Fig. 1, *A*) taken fourteen hours after hospital admission revealed a bilateral peribronchial infiltration with peripheral emphysema, more marked on the right. He was placed in an oxygen tent and given intravenous fluids and blood. Intravenous penicillin was started immediately. The patient remained critically ill for one week with marked dyspnea, shallow respirations, and tachypnea. The temperature spiked from 103° to 105° F., one to two times daily for seven days, then gradually returned to normal by the tenth hospital day. On the fourth day, chest radiograph (Fig. 1, *B*) showed more extensive peribronchial infiltration and persistent emphysema. The white blood cell count on the second hospital day was 13,400 with 65 per cent polymorphonuclears.

In spite of immediate hospitalization and prophylactic antibiotic therapy, this patient was critically ill for a week. The quantity of red furniture polish consumed was unusually large and here again ample opportunity for aspiration was present.

Case 6.—C. S., a 16-month-old Negro male, consumed an unknown quantity of "Old English" red furniture polish. The parents induced vomiting immediately by digital gagging. This was associated with much coughing and struggling. The patient rapidly developed lethargy, pallor, and cold, clammy skin. He arrived in the emergency room within two hours. Examination revealed a semicomatose infant with marked dyspnea, flaring alae nasae, and rhonchi. No râles were heard on auscultation over both lung fields. Admitting chest radiograph (Fig. 2, *A*) showed only generalized emphysema. The patient was admitted to the hospital, placed in an oxygen tent, and given stimulants and antibiotics. In spite of this, he remained critically ill. White blood cell count varied from



A. *B.*

Fig. 2.—C. S. *A*, At two hours after ingestion, the child was semicomatose but the chest was clear except for emphysema. *B*, Three days after admission and three days before death, there was an extensive confluent pneumonitis, but the periphery was still clear.

33,900 on admission to 17,200 just prior to death, with 90 to 92 per cent polymorphonuclears. Hemoglobin was 10.0 Gm. per cent. Urinalysis was negative. His temperature rose to 102° F., respiration to 120, and the heart rate to over 200 as confirmed by electrocardiogram. Chest radiograph on the third hospital day (Fig. 2, *B*) revealed a massive infiltration, rather irregular in distribution but maintaining a clear zone peripherally. On the sixth hospital day, frank pulmonary consolidation appeared; the pulse rose to 240 per minute, all measures to control temperature and dyspnea failed, and the patient expired. Permission for post-mortem examination was not granted.

Vigorous digital gagging and induced emesis associated with coughing and choking preceded this patient's admission to the hospital. The marked leukocytosis was seen repeatedly in the more seriously ill patients, and seemed to appear with great rapidity.

Case 9.—B. L. J., a 12-month-old Negro female patient, was admitted to the hospital twenty-four hours following the ingestion of three to four ounces of "O'Cedar" red furniture polish. The parents stated that immediately following the ingestion of furniture polish, she had "coughed and strangled" for twenty to thirty minutes. She was then given a glass of milk, following which she vomited a mixture of the polish and milk. The patient was seen by a physician who administered an emetic. The patient again vomited, but did not appear ill, and returned home. However, when again seen by the physician twelve hours later, the patient had a temperature of 101° F., was oliguric, and appeared critically ill. She was referred to the Jefferson Davis Hospital emergency room and admitted to the hospital. Admitting chest radiograph showed bilateral bronchopneumonia. Examination in the hospital revealed an acutely ill infant in severe respiratory distress, with flaring of the alae nasae, and grunting, shallow, rapid respirations and a pulse rate of 166 per minute. Her skin was hot and dry. Auscultation of the chest revealed no evidence of pulmonary disease. The patient was given parenteral antibiotics, parenteral fluids, and placed in an oxygen tent. Temperature on admission was 100.2° F., rapidly rising to 103° F., and remaining at this level until the patient expired in coma on the third hospital day.

Necropsy Findings: Examination was performed nine hours after death. Significant gross and microscopic changes were confined to the thoracic cavity. There were emphysematous blebs throughout the mediastinum. The pleural surfaces were smooth and glistening and no fluid was present in the pleural cavities. The lungs, together, weighed 400 grams. Their pleural surfaces were mottled dark red and blue. Along the anterior border of the left upper lobe were emphysematous blebs up to 1.0 cm. in diameter. The peripheral portions of both upper lobes were crepitant. The lower lobes were firm and rubbery. Cut surfaces of the upper lobes were similar in their medial portions. Peripherally, the cut surfaces were fairly dry and the air spaces were visible. The bronchi and bronchioles contained abundant, thick, pale yellow, mucoid material.

Microscopically, all preparations of lung revealed similar changes (Fig. 3). Most of the alveoli contained abundant pink-stained coagulum, with enmeshed macrophages and scattered cellular debris. Thick hyaline membranes lined many of the air spaces. The capillaries of the septa were distended with erythrocytes, as were the larger blood vessels elsewhere. Scattered foci of necrosis were present. Most of the bronchioles contained pink-stained coagulum. In many, the lining epithelium was shed. There was interstitial edema throughout the peribronchiolar tissues with fairly dense

infiltrations of lymphocytes, plasma cells, and less numerous macrophages and neutrophilic granulocytes. Scarlet red stains on frozen sections of formalin-fixed tissue revealed minute particles and globules of stained material within the coagulum in the alveoli and particularly within the cytoplasm of many of the macrophages.

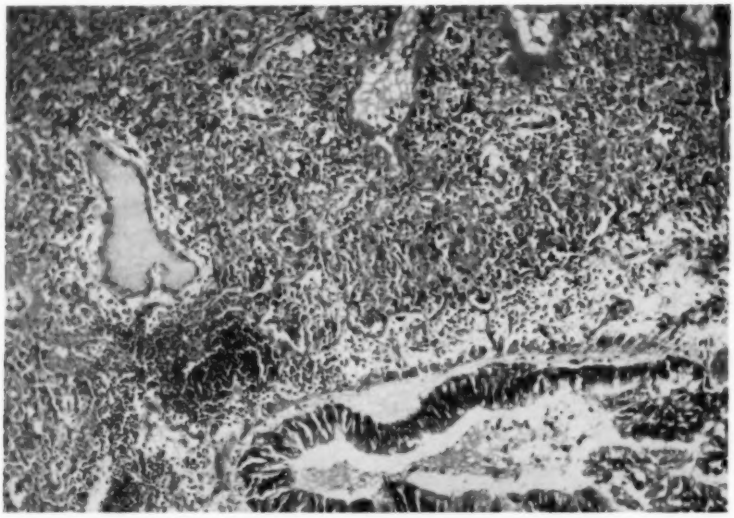


Fig. 3.—Section of lung. There is prominent exudate in the lumens of the alveoli and bronchioles and in the interstitial tissue. In some of the alveoli, the exudate is inspissated, forming hyaline membranes. The inflammatory infiltrate consists largely of lymphocytes, plasma cells, and macrophages.

Anatomic Diagnoses: Confluent bronchopneumonia involving all lobes of the lungs; hyperemia and edema of the lungs; emphysema of the lungs, upper lobes; emphysema of mediastinum.

Again, induced emesis was conspicuous and the onset of symptomatology was rapid. The necropsy findings are those of an extensive aspiration pneumonitis.

CLINICAL FINDINGS

The mean age of 17 months and the age range of 11 to 24 months noted in our patients is the age group in which accidental poisonings are most frequent. No significant sex difference was noted; the series contained ten males and five females. The predominance of Negro over white children is representative of this hospital's population. As noted in Table I, the quantity of furniture polish ingested tended to be appreciable, varying from one-half to four ounces. Although the exact brand name was not included in the history of some cases, all patients were known to have taken a red furniture polish. All of the children we have seen following the ingestion of red furniture polish have developed significant pulmonary disease. Coughing and gagging were clearly established in eleven cases and were indefinite in four cases. Spontaneous vomiting or gastric lavage was described in nine cases. In the two fatal cases, vomiting was induced by vigorous digital manipulation. These were the only patients in which this procedure was employed.

In six cases, there was no history of vomiting or lavage. Although the presenting symptoms were usually those of a disturbed sensorium, the pulmonary disease was the major factor in the duration and severity of the patient's illness. Nine patients were described as definitely lethargic; three were described as semicomatose and one as comatose within a period of a few minutes to several hours after ingestion of the furniture polish. These changes usually preceded any respiratory or systemic signs and symptoms and, except for the two fatal cases, were transient in duration. The lapse of time from consumption of the furniture polish to the appearance of temperature elevation ranged from two to forty-eight hours, with a median range of five to twelve hours. The febrile course was characterized by spiking temperatures of 102° to 106° F., lasting from one to nineteen days, with a mean duration in the nonfatal cases of approximately seven days.

Among clinical laboratory studies performed, it is noteworthy that the initial white blood cell count revealed marked leukocytosis in eight of the twelve cases. A left shift in the differential was a relatively consistent finding. Several patients were moderately anemic, but the relation of this finding to their hydrocarbon ingestion is probably not significant. The anemia was invariably present at the time of admission and is a relatively common finding among the patients attending our clinic. Urinalyses were for the most part negative. One severely ill patient (Case 6), who subsequently expired, showed a 2+ albumin, 4+ acetone, and the microscopic examination revealed large numbers of free fat droplets. In the same patient the HCO_3 content was 17.5 meq. per liter, but this isolated observation probably reflects only the critical state of the patient, with accumulation of ketones and other organic acids in the immediate ante-mortem period.

RADIOGRAPHIC FINDINGS

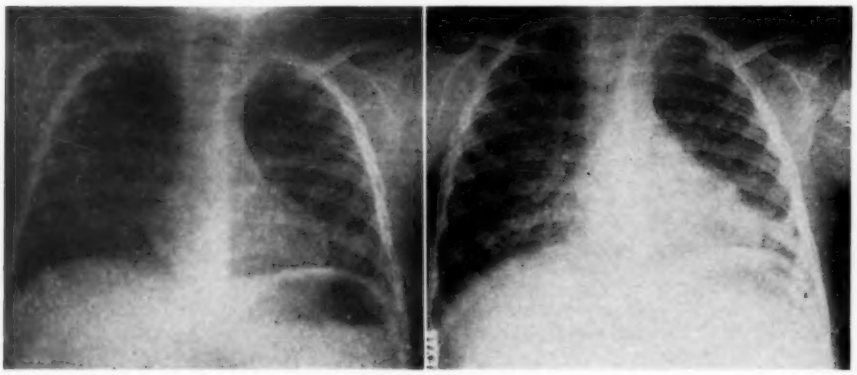
The outstanding radiographic feature is the delayed appearance of the gross inflammatory changes in the lung fields. Although the child may be acutely ill or in mild collapse, respiratory signs and symptoms are not prominent and the initial chest film, usually taken within two hours of the time of ingestion, is likely to be deceptively clear (Figs. 2, *A* and 4, *A*). There may be a mild generalized emphysema, or a more evident degree of hyperaeration of only a portion of the lung field. Because of the reassuring appearance of the initial film, the examination may not be repeated until the second day, when respiratory signs and symptoms have become prominent. However, as early as two hours after ingestion, films may show the development of a symmetrical pneumonitis extending out from the hilar regions to involve the medial portions of both lung fields (Fig. 5, *A* and *B*). Occasionally, a local area of emphysema in the periphery may stand out (Fig. 6). The peak of the reaction is likely to be achieved about the third day (Fig. 2, *B*), with extension of the inflammatory process to involve the medial half or medial two-thirds of both lung fields. The appearance is not that of atelectasis or lobar consolidation. The increased density is coarsely punctate (Figs. 1, *B* and 4, *B*), with a tendency to confluence in the hilar or paramediastinal regions while preserving a clear zone of peripheral emphysema. The distribution is that of a chemical pneu-

monitis in which the initial inflammatory response in the bronchial mucosa is insufficient to be apparent on the film, but may cause some degree of obstructive emphysema (Figs. 1, *A*, 2, *A*, and 5, *A*). The inflammatory changes become evident in the film as the process extends to involve the wall of the bronchi and bronchioles and the peribronchial tissues. This accounts for the punctate character of the involved area, and increasing congestion and edema results in some coalescence.

The persistence of the pneumonitis is variable, but always longer than the clinical manifestations. Resolution may be evident within a week, but in severe cases may not be certain until the second week. Complete clearing may require three to six weeks. No

A. *B.*

Fig. 4.—M. W. *A*, A film taken two hours after ingestion shows only mild peribronchial infiltration. No further radiographs were taken, and the patient left the hospital against medical advice after forty-eight hours. *B*, One day later, the patient was readmitted and an extensive peribronchial infiltration was demonstrated.



A. *B.*

Fig. 5.—C. McC. *A*, The initial film taken approximately one-half hour after ingestion showed only emphysema more marked on the right side. *B*, Two hours later, the peribronchial inflammatory infiltration was demonstrated.

residual changes have been noted to suggest either bronchiectasis or areas of chronic lipoid pneumonia (Fig. 7, *A* and *B*).

LITERATURE

The literature concerning hydrocarbon ingestion and intoxication is extensive.[5-10] Of the hydrocarbons described, kerosene has been the most frequently observed offender.[3]

Many studies have amply demonstrated that small amounts of aspirated kerosene produce rather extensive pulmonary changes in experimental animals.[3, 4, 5, 6, 7] That pneumonia may also result from excretion of the ingested kerosene through the lungs, after absorption of this hydrocarbon from either the gastrointestinal tract or the peritoneal cavity, has been demonstrated.[6, 7] Deichmann and associates,[6] using intraperitoneal injections of kerosene in adult rabbits, were able to produce typical pneumonia. Richardson and Pratt-Thomas[7] emphasize the quantitative aspects of this prob-

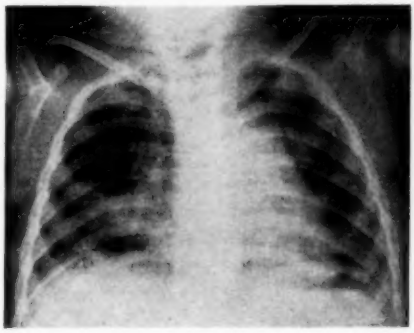
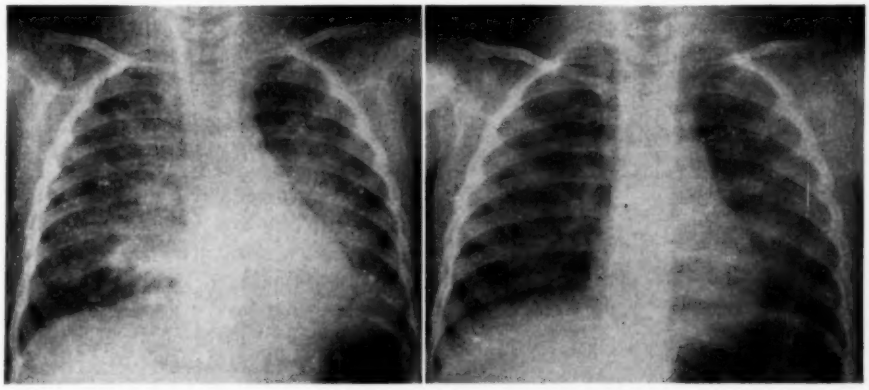


Fig. 6.—M. A. E. A film taken eighteen hours after ingestion shows obstructive emphysema of right upper lobe in addition to pneumonitis.



A. *B.*

Fig. 7.—D. B. D. *A*, At one week after ingestion, the pneumonitis was at its height. The infiltration was confluent centrally and there was peripheral obstructive emphysema. *B*, A follow-up film taken six months later showed no evidence of residual pulmonary damage.

lem in extensive animal studies. They found that, whereas 0.25 c.c. per kilogram of kerosene injected into the trachea of a rabbit produced fulminating and fatal pulmonary parenchymal necrosis in two and one-half days, 35 c.c. per kilogram by intragastric tube was required to produce fatal pulmonary changes in four days. From this observation, they conclude that it would be difficult to conceive of a child's drinking a sufficient quantity of kerosene to prove fatal solely by absorption from the gastrointestinal tract and excretion through the lungs. If the values obtained in these experimental studies can be applied to the human subject, a child weighing 10.0 kilograms would have to ingest 350 c.c. of kerosene to receive a lethal dose. In contrast, 2.5 c.c. of kerosene aspirated by this child into his trachea would constitute a fatal quantity.

Similar definitive studies have not been carried out using other commonly available hydrocarbons (e.g., naphtha, gasoline, lighter fluid, and mineral seal oil).

TREATMENT

The problem surrounding the immediate therapy of patients having ingested hydrocarbon products has been the subject of much debate in the medical literature. The most critical experimental studies supported the importance of aspiration and deemphasized the possible contribution of "excretory pneumonitis." Our extensive experience with patients who have ingested kerosene suggests that the excretory route is not clinically significant. Consequently, in this hospital, gastric lavage and induced vomiting are avoided at the present time. Our experience with furniture polish pneumonitis is more limited, but it is worthy of note that the only two deaths in this series occurred in patients who, after ingesting furniture polish, were treated by vigorous induced emesis and gastric lavage. Clinical experience leads us to believe that gastric lavage cannot be performed consistently without the presence of some gagging and opportunity for aspiration by the patient. The use of catharties in patients known to have taken large amounts of hydrocarbon products may be of some theoretical value and appears to be without hazard.

The routine administration of prophylactic antibiotics for three to four days, or until such time as the radiograph is negative, seems to be a well-established and important precept. Case 11 pointedly emphasizes this fact. Forty-eight hours after the ingestion of furniture polish, this patient left the hospital against medical advice. While in the hospital, the patient was on antibiotic therapy, although afebrile and relatively asymptomatic. No therapy was continued at home. Twenty-four hours after leaving the hospital, she was returned in a critical condition with extensive pneumonia, high temperature, and marked leukocytosis. She remained critically ill for about seven days, then slowly improved and was discharged on the eighteenth hospital day.

Symptomatic supportive therapy was used as indicated by the individual patient's needs. This included humidified oxygen, stimulants, parenteral fluids, and whole blood transfusions.

DISCUSSION

It becomes apparent from the observed morbidity and mortality in these cases of red furniture polish

pneumonia that the clinical disease is of greater severity than that usually seen in the more commonly observed kerosene pneumonia. Several possibilities exist which may in whole or in part be the factors involved in this more critical clinical course. First, mineral seal oil is a heavier "cut" than the gasoline-kerosene fraction and is more nearly similar to a light lubricating oil. This suggests that it might act both as a pulmonary irritant and as a foreign body in the lung, thus giving signs and symptoms similar in some respects, to both kerosene pneumonia and lipoid pneumonia. It is interesting to note, in this light, that the three patients (Cases 7, 8, and 13) known to have taken a product composed of only 20 per cent mineral seal oil and 80 per cent kerosene, were less ill than those patients in the series known to have taken a product composed almost entirely of mineral seal oil; the symptomatology and clinical course was not significantly different from that of a typical kerosene pneumonia.[3] A second possible explanation for the observed severity of the course of these patients in contrast to the course of those with kerosene pneumonitis is a finding repeatedly noted by the house staff. Whereas the patient ingesting kerosene is described by his parents as drinking not more than one swallow and immediately rejecting the rest, the parents of the patients who have taken red furniture polish consistently characterize the amount taken as one-half to one cupful. This may be due in part to the fact that red furniture polish has an enticing odor, is slightly flavored, and, though flat, is not unpleasant to the taste. The larger quantity of furniture polish usually ingested by these patients offers opportunity for aspiration of a greater quantity and could reasonably account, quantitatively, for the more severe clinical course. A third factor which may contribute to the severity of the pneumonia is the presence of small quantities of coloring and odorizing agents in some of these products. These products may be in themselves unusually irritating (e.g., methyl salicylate); however, the very small quantity of these materials ingested in comparison to the total volume of furniture polish suggests that the role of such agents is a minor one at most.

The reaction of the lung to oils and fats was carefully studied and reported by Pinkerton.[8, 9] He was among the first to call attention to the syndrome of "cod-liver oil pneumonia," as a result of aspiration occurring in debilitated children confined to bed. He demonstrated by experimental studies that cod-liver oil, chaulmoogra oil, and lard oils (animal fats) produced an acute inflammatory process with edema and necrosis of the pulmonary parenchyma. Conversely, vegetable oils produced a mild reaction. He related the degree of acute necrotizing reaction to the presence in these compounds of a high percentage of unsaturated hydrocarbons. The ability of the compound to undergo hydrolysis rapidly in the lungs to form fatty acids was also thought to be a significant factor.

The pathologic changes present in the lungs of one fatal case (Case 9) appear to be characteristic of "chemical pneumonitis," both with regard to the distribution of the lesions and the character of the inflammatory reaction. The reaction in its fully developed state is exudative, with a

moderate infiltration of inflammatory cells principally in the interstitial and peribronchial tissues, consisting predominantly of mononuclear cells. The exudate is rich in protein and there is a prominent tendency for the alveoli to have a hyaline lining. Small areas of necrosis may be present in the more involved portions of the lung. Obstructive or compensatory emphysema is likely to develop. (The findings characteristic of a lipoid pneumonia were not present in this patient.)

SUMMARY

1. The clinical findings in fifteen children who ingested red furniture polish are presented. Red furniture polish is composed principally of a petroleum hydrocarbon known commercially as mineral seal oil.

2. These patients all developed pneumonitis and, in general, the course of their illness was more severe than the course usually observed in children who ingest other hydrocarbon products such as kerosene or lighter fluid.

3. Two deaths occurred in this group of fifteen children. The necropsy findings in one of the fatal cases are presented.

4. The initial radiographic finding may only be a generalized emphysema. At about two hours, the developing peribronchial infiltration becomes evident, and as it mounts, the preservation of a clear zone of peripheral emphysema is distinctive. The inflammatory process reaches its height about the third day and resolution may require a period of three to six weeks.

5. In the management of these patients, gastric lavage and induced vomiting should be avoided because of the danger of aspiration during the procedure. Treatment should consist of prophylactic antibiotics and general supportive measures.

Grateful acknowledgment is made to the University of Texas Post-Graduate School of Medicine for permission to use the pathological material from the necropsy of patient 9. We also wish to express our appreciation to the following physicians for permission to use their cases: Dr. Russell J. Blattner (Case 10) and Dr. D. C. Carrington, Jr. (Case 11).

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DIETARY FRUCTOSE IN CHILDREN WITH DIABETES MELLITUS

ALEXIS F. HARTMANN, SR., M.D., HULDA J. WOHLTMANN, M.D., AND
ALEXIS F. HARTMANN, JR., M.D.
ST. LOUIS, MO.

THE fact that fructose can be phosphorylated and enter the carbohydrate cycle (Fig. 1) without the assistance of insulin has stimulated renewed interest in the possibility that fructose might play an advantageous role in diabetic control. So far, recent work has been concerned chiefly with immediate or very early metabolic effects of intravenously introduced fructose and not with any later influence when incorporated into the diet. It occurred to us that the diabetic child, whose course is usually one of rapid loss of tolerance during the first few years and then stabilization at a level of total or near-total diabetes (Fig. 2), would be a better subject than the usual milder and less stabilized adult for investigating whether or not appreciable amounts of orally ingested fructose could be utilized over an extended period without the need for insulin.

The method of assessing and recording severity and stability of diabetes mellitus of children attending the clinic at the St. Louis Children's Hospital rests upon the determination of the daily apparent metabolic glucose/insulin ratios, as pictured in Figs. 2 and 3. Many years of experience with this method have demonstrated that almost all healthy well-regulated children, after a few years of diabetes, will have G/I ratios between the low of 2 and the high of 10, and remain remarkably constant for long periods provided that glycosuria is maintained at a level of no more than 5 per cent of the total available glucose in the diet and provided also that infections, emotional upsets, and hypoglycemia are avoided and that exercise is not permitted to vary greatly from day to day without appropriate dietary or insulin adjustment.

Five children were selected whose records indicated continued good control, normal physical status and growth rate, and stabilized severity at the level of total or near-total diabetes on the standard diet which provided 15 per cent of the calories from protein, 35 per cent from carbohydrate, and the remainder, 50 per cent, from fat.

To investigate whether or not appreciable amounts of fructose could be incorporated into and later removed from the diet with substitution of isocaloric amounts of glucose and sucrose without change in insulin requirements, new diets were constructed to provide as nearly as possible the following:

- 15 per cent of total calories from natural proteins (chiefly meat, eggs, and milk)
- 40 per cent of total calories from natural fats
- 20 per cent of total calories from natural carbohydrates
- 25 per cent of total calories from purified fructose, glucose, or sucrose.

With assistance from Mead Johnson & Company.

From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

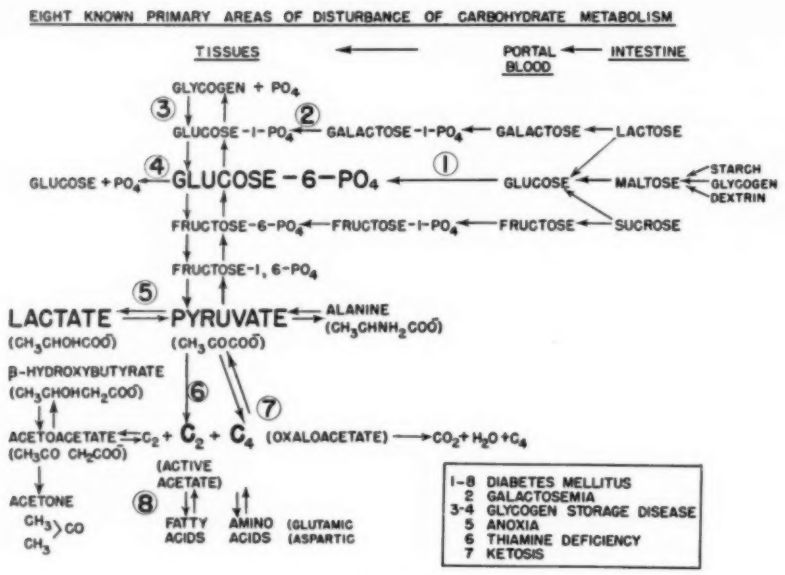

EIGHT KNOWN PRIMARY AREAS OF DISTURBANCE OF CARBOHYDRATE METABOLISM
TISSUES
PORTAL BLOOD
INTESTINE
GLYCOGEN + PO4
GLUCOSE-1-PO4
GALACTOSE-1-PO4
GALACTOSE
LACTOSE
GLUCOSE + PO4
GLUCOSE-6-PO4
GLUCOSE
MALTOSE
STARCH
GLYCOGEN
DEXTRIN
FRUCTOSE-6-PO4
FRUCTOSE-1-PO4
FRUCTOSE
SUCROSE
FRUCTOSE-1, 6-PO4
LACTATE
(CH3CHOHCOO)
PYRUVATE
(CH3COCOO)
ALANINE
(CH3CHNH2COO)
β-HYDROXYBUTYRATE
(CH3CHOHCH2COO)
ACETOACETATE
(CH3CO CH2COO)
(OXALOACETATE)
CO2 + H2O + C4
(ACTIVE ACETATE)
ACETONE
FATTY ACIDS
AMINO ACIDS
(GLUTAMIC
(ASPARTIC
1-8 DIABETES MELLITUS
2 GALACTOSEMIA
3-4 GLYCOGEN STORAGE DISEASE
5 ANOXIA
6 THIAMINE DEFICIENCY
7 KETOSIS

Fig. 1.

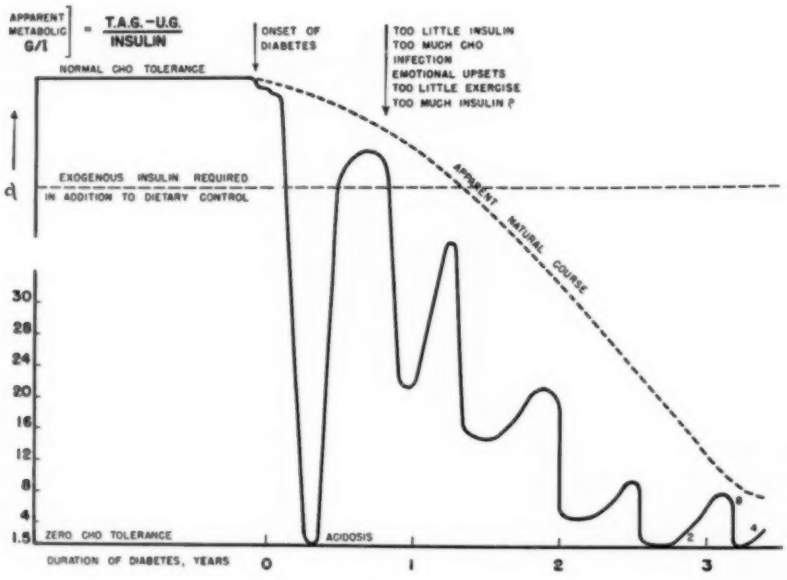

APPARENT METABOLIC G/I = T.A.G. - U.G. / INSULIN
ONSET OF DIABETES
TOO LITTLE INSULIN
TOO MUCH CHO
INFECTION
EMOTIONAL UPSETS
TOO LITTLE EXERCISE
TOO MUCH INSULIN ?
NORMAL CHO TOLERANCE
EXOGENOUS INSULIN REQUIRED IN ADDITION TO DIETARY CONTROL
APPARENT NATURAL COURSE
30
28
24
20
16
12
8
4
1.5
ZERO CHO TOLERANCE
ACIDOSIS
DURATION OF DIABETES, YEARS
0
1
2
3

Fig. 2.

Total available glucose (TAG) was calculated for each diet on the assumption that 100 per cent of all carbohydrate (natural food, fructose, glucose, sucrose) was potential glucose and that 58 per cent of protein and 10 per cent of fat also were potential glucose. So far as possible, no changes were made in the child's daily life other than the dietary changes. To avoid possible seasonal influences, dietary switches were made every few weeks. Data are tabulated in Tables I to V, inclusive, on a daily basis and graphed as approximately weekly averages (Figs. 4 to 10).

period, ratios varied between 8.7 and 10, averaging 9.5. Then two weeks on the glucose diet without change in insulin dosage showed ratios of 10. Switch for two weeks to fructose gave very similar ratios, ranging from 9.5 to 10.3 and averaging 9.9. Switches to sucrose for two weeks, then to glucose for a similar period, then back to sucrose, then to glucose, to sucrose, back to glucose, and finally again to fructose were attended by unchanged and remarkably constant ratios.

Throughout the entire study period, control was good, and because some glycosuria was always present and no insulin reactions had occurred, it seems reasonable to conclude that at no time was insulin administered in excess of

METABOLIC GLUCOSE/INSULIN RATIO

EQUALS

$$\frac{\text{TOTAL AVAILABLE GLUCOSE—URINARY GLUCOSE}}{\text{INSULIN}}$$

Fig. 3.

CASE REPORTS

CASE 1.—Andrew L. This boy was 11 years old at the time of these studies. His diabetes began at the age of 3½, late in 1945. After hospital admission for confirmation of diagnosis and regulation in January, 1946, he showed early gain in tolerance which permitted him to go without insulin for several weeks in February, 1946. Secondary loss of tolerance then was noted, with some fluctuation of severity from time to time. Control remained excellent, and physical progress was very good as demonstrated by his Wetzel Grid (Fig. 4, *B*).

Prior to the present studies, he showed stabilization at a 7 to 9 ratio when on the standard diet yielding 2,700 calories and 375 grams total available glucose. During the first week of study when sucrose supplied 25 per cent of the total calories, the G/I ratio remained steady and averaged 9.1. After substitution of fructose for sucrose, over a three-week

actual need. If the late results of fructose metabolism were such as to be without the need of insulin, the fructose diets could have been considered as yielding 207 grams potential glucose instead of 375. The difference, 168 grams, should then have allowed for reduction of approximately 16.8 units of insulin since the apparent metabolic G/I ratio was 10. Instead, no reduction of insulin was possible, and the G/I ratio, which, theoretically, could have increased to approximately 19.7, remained at 10.

These very clear-cut results, therefore, strongly suggest that dietary fructose cannot be substituted for glucose with any sparing of insulin requirement.

CASE 2.—Mildred G. This girl was born on Dec. 23, 1939, being almost 14 years old at the time of the study. The first-born child in the family developed diabetes at the age of 3. The second-born, a girl now 16, is nondiabetic. The patient, the third-born

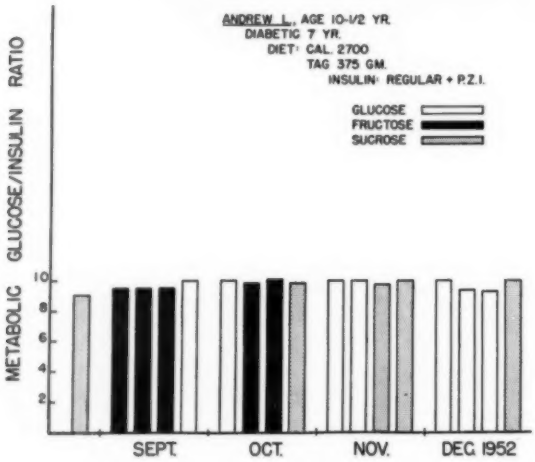
TABLE I. ANDREW L.: AGED 11 YEARS; DIET 2,708 CALORIES; 375 GRAMS TAG; G/I 7 TO 9

FRUCTOSE PERIODS				SUCROSE PERIODS				GLUCOSE PERIODS			
DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/24 HR.	G/I	DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/24 HR.	G/I	DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/24 HR.	G/I
1952				*1952*				*1952*			
8/30	36.0	26/13	8.7	8/23	1 wk. 5-15	26/13	8.2-9.2	9/22	½-1%	24/12	Incomplete, in school
8/31	24.8	24/12	9.4	8/24	24.5	26/13	9.0	9/23	0-2%	24/12	
9/ 1	11.4	24/12	10.0	8/29	25.6	26/13	9.0	9/24	1-3%	24/12	
9/ 4	10.2	24/12	10.0					9/25	1-2%	24/12	
9/ 8	25.3	24/12	9.4	10/20	9.0	24/12	10.0	9/26	0-2%	24/12	
9/13	11.8	24/12	10.0	10/21	½-1%	24/12		9/27	11.8	24/12	10.0
9/14	39.7	24/12	9.0	10/22	½-1%	24/12		9/28	8.3	24/12	10.0
9/20	18.5	24/12	9.9	10/23	½-1%	24/12		9/29	½-2%	24/12	Incomplete, in school
9/21	23.4	24/12	9.3	10/24	1-2%	24/12		9/30	0-1%	24/12	
				10/25	2%	24/12		10/ 1	1-3%	24/12	
10/ 5	11.5	24/12	10.0	10/26	17.6	24/12	9.8	10/ 2	2%	24/12	
10/ 6	30.3	24/12	9.5	10/27	0-1%	24/12		10/ 3	½-2%	24/12	
10/ 7	0-2%	24/12		10/28	1%	24/12		10/ 4	14.2	24/12	10.0
10/ 8	1-2%	24/12		10/29	0-1%	24/12					
10/ 9	½-1%	24/12		10/30	1-2%	24/12		11/ 3	0-2%	24/12	
10/10	1-3%	24/12		10/31	1-2%	24/12		11/ 4	0-2%	24/12	
10/11	19.8	24/12	9.9	11/ 1	34.3	20/16	9.5	11/ 5	½-2%	24/12	
10/12	1-2%	24/12		11/ 2	17.0	24/12	10.0	11/ 6	0-2%	24/12	
10/13	1-2%	24/12						11/ 7	0	24/12	(Slight reaction)
10/14	0-1%	24/12		11/16	29.7	24/12	9.6	11/ 8	8.8	24/12	10.0
10/15	0-1%	24/12		11/17	1-3%	24/12		11/ 9	20.6	24/12	9.9
10/16	1-2%	24/12		11/18	½-3%	24/12		11/10	0-2%	24/12	
10/17	1%	24/12		11/19	1-6%	24/12		11/11	13.4	24/12	10.0

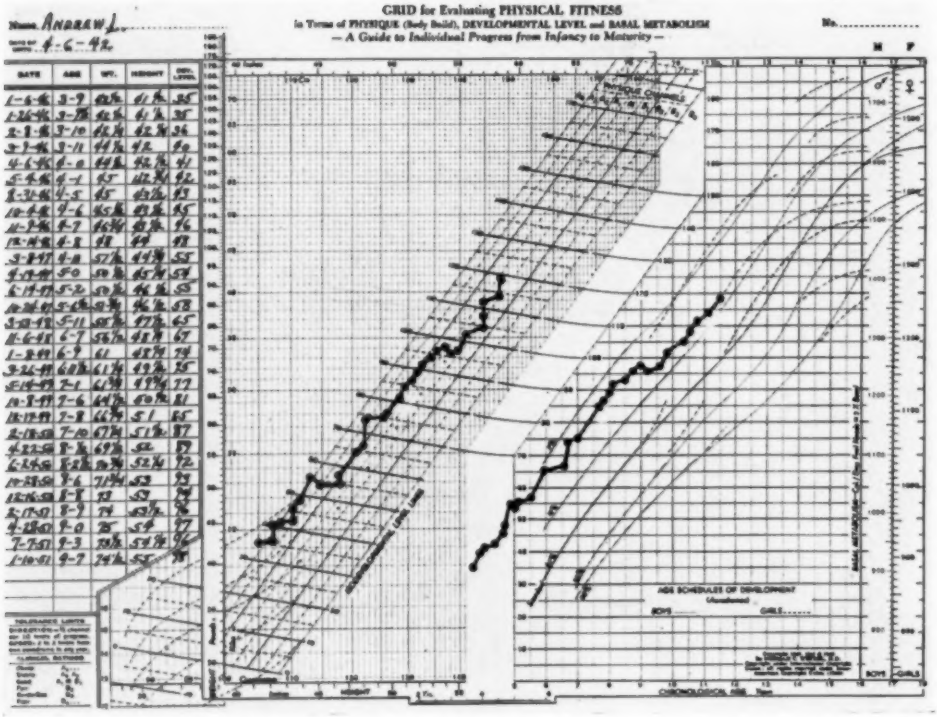
10/18	14.5	24/12	10.0
10/19	2.35	24/12	10.3
1953			

11/20	0·1%	24/12	
11/21	0·2%	24/12	
11/22	14.2	24/12	10.0
11/23	18.3	24/12	10.0
11/24	2·3%	24/12	
11/25	1·2%	24/12	
11/26	1·2%	24/12	
11/27	13.7	24/12	10.0
11/28	0·2%	24/12	
12/11	1·3%	24/12	
12/12	1·3%	24/12	
12/13	0·3%	24/12	
12/26	tr.·2%	26/13	
12/27	1·3%	26/13	
12/28	1·2%	26/13	
12/29	0·2%	26/13	
12/30	0·2%	26/13	
12/31	tr.·1%	26/13	
1953			
1/ 1	0·1%	26/13	
1/ 2	12.6	26/13	10.0

11/12	1·3%	24/12	
11/13	0·2%	24/12	
11/14	0·3%	24/12	
11/15	0·2%	24/12	
11/29	½·2%	24/12	
11/30	14.5	24/12	10.0
12/ 1	½·1%	24/12	
12/ 3	½·3%	24/12	
12/ 4	0·2%	24/12	
12/ 5	0·3%	24/12	
12/ 6	1·3%	24/12	
12/ 7	15.8	24/12	10.0
12/ 8	0·2%	24/12	
12/ 9	0·2%	24/12	
12/10	1·3%	24/12	
12/14	29.1	24/12	9.3
12/15	20.4	24/12	9.6
12/16	½·1%	24/12	
12/17	0·3%	24/12	
12/18	1·3%	24/12	
12/19	2·3%	24/12	
12/20	29.7	24/12	9.3
12/21	1·2%	26/13	
12/22	0·3%	24/12	
12/23	1·3%	26/13	
12/24	tr.·2%	26/13	
12/25	6.9	26/13	9.4
1953			

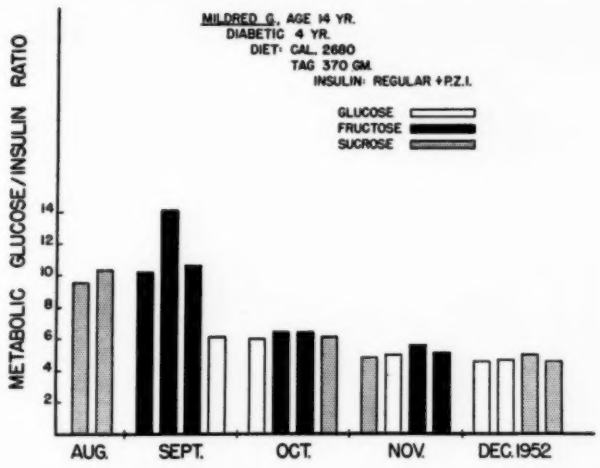

ANDREW L., AGE 10-1/2 YR.
DIABETIC 7 YR.
DIET: CAL. 2700
TAG 375 GM.
INSULIN: REGULAR + P.Z.I.
GLUCOSE
FRUCTOSE
SUCROSE
METABOLIC GLUCOSE/INSULIN RATIO
10
8
6
4
2
SEPT.
OCT.
NOV.
DEC. 1952

A.

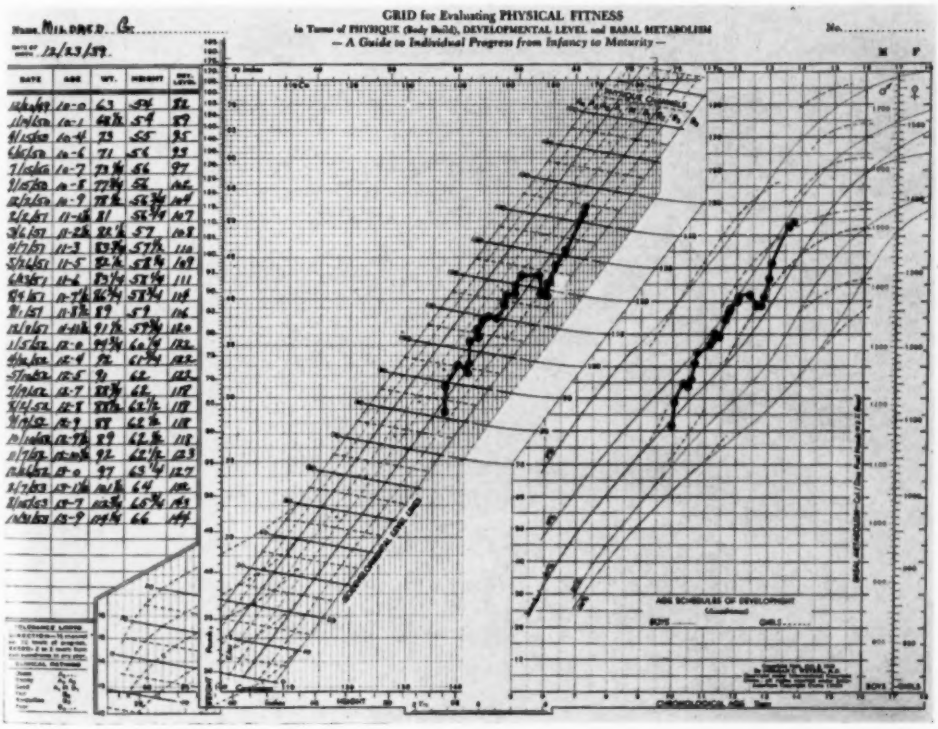

GRID for Evaluating PHYSICAL FITNESS
in Terms of PHYSIQUE (Body Build), DEVELOPMENTAL LEVEL and BASAL METABOLISM
— A Guide to Individual Progress from Infancy to Maturity —
Name Andrew L.
Date 4-6-42
No.
M F
DATE AGE WT. HEIGHT DEV. LEVEL
1-6-41 3-9 40¾ 41 ¾ 35
1-26-41 3-10 42 ¾ 41 ¾ 35
2-8-41 3-10 42 ¾ 42 ¾ 34
3-7-41 3-11 44 ¾ 42 40
4-6-41 4-0 44 ¾ 42 ¾ 41
5-4-41 4-1 45 42 ¾ 42
5-31-41 4-5 45 43 ¾ 43
10-4-41 4-6 45 ¾ 43 ¾ 45
11-2-41 4-7 46 ¾ 43 ¾ 46
12-14-41 4-8 48 44 48
3-2-42 4-8 47 ¾ 44 ¾ 53
4-13-42 5-0 50 ¾ 45 ¾ 54
6-19-42 5-2 50 ¾ 46 ¾ 55
10-26-42 5-6 52 ¾ 46 ¾ 58
3-10-43 5-11 52 ¾ 47 ¾ 65
11-6-43 6-7 56 ¾ 48 ¾ 67
1-2-44 6-9 61 48 ¾ 78
3-24-44 6-8 ¾ 61 ¾ 49 ¾ 75
5-14-44 7-1 61 ¾ 49 ¾ 77
10-3-44 7-6 64 ¾ 50 ¾ 81
12-19-44 7-8 66 ¾ 51 85
2-12-45 7-10 67 ¾ 51 ¾ 87
4-22-45 8-¼ 69 ¾ 52 89
6-24-45 8-2 ¾ 70 ¾ 52 ¾ 92
10-23-45 8-6 71 ¾ 53 93
12-26-45 8-8 73 53 96
2-17-47 8-9 74 53 ¾ 96
4-28-47 8-10 75 54 97
7-7-47 9-3 77 ¾ 54 ¾ 96
1-10-47 9-7 74 ¾ 55 98
Constitutional Line
Physique Channels
Age Schedules of Development
Boys
Girls
Basal Metabolism
Chronological Age

B.

Fig. 4.


MILDRED G. AGE 14 YR.
DIABETIC 4 YR.
DIET: CAL. 2680
TAG 370 GM.
INSULIN: REGULAR + P.Z.I.
GLUCOSE
FRUCTOSE
SUCROSE
METABOLIC GLUCOSE/INSULIN RATIO
14
12
10
8
6
4
2
AUG.
SEPT.
OCT.
NOV.
DEC. 1952

A.


GRID for Evaluating PHYSICAL FITNESS
in Terms of PHYSIQUE (Body Build), DEVELOPMENTAL LEVEL and BASAL METABOLISM
— A Guide to Individual Progress from Infancy to Maturity —
Name MILDRED G.
No.
DATE
AGE
WT.
HEIGHT
DEV. LEVEL
ABS SCHEDULES OF DEVELOPMENT
BOYS
GIRLS
CHRONOLOGICAL AGE

B.

Fig. 5.

TABLE II. MILDRED G.: AGED 14 YEARS; DIET, 2,680 CALORIES; 370 GRAMS TAG; G/I 8 TO 10

FRUCTOSE PERIODS				SUCROSE PERIODS					GLUCOSE PERIODS			
DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/24 HR.	G/I	DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/24 HR.	G/I		DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/24 HR.	G/I
1952				*1952*					*1952*			
8/30	24.8	22/11	10.0	8/ 7	117.0	20/10	9.0					
8/31	0 (incomp.)	22/11		8/ 8	110.4	22/11	8.0					
9/ 1	1.0	22/11	11.0	8/11	30.0	24/12	9.0		9/25	43.5	24/12	9.0
9/ 2	0 (incomp.)	20/10		8/12	0	24/12	10.0	? Reaction	9/26	Incomplete		
9/ 3	11.2	20/10	10.0	8/13	0	24/12	10.0		9/27	75.6	28/14	6.6
9/ 4	0 (incomp.)	20/10		8/14	0	22/11	11.0		9/28	42.0	30/15 + 5	6.5
9/ 5	0 (incomp.)	20/10		8/15	6.0	22/11	11.0		9/29	55.6	32/16 + 5	6.9
9/ 6	0	18/ 9	14.0	8/16	30.0	22/11	10.3		9/30	24.7	34/17 + 5	5.0
9/ 7	14.7	16/ 8	14.8	8/18	0	22/11	11.0		10/ 1	136.5	36/18 + 25	4.0
9/8 to 9/12	incomp.—in school			8/19	45.0	20/10	10.8		10/ 2	35.5	40/20 + 5	5.0
				8/23	40.5	22/11	10.0		10/ 3	3.45	38/19	6.4
9/13	0	18/ 9	13.7	8/25	39.5	22/11	10.0		10/ 4	12.0	40/20	6.0
9/14 to 9/17	incomp.—in school			8/27	23.2	22/11	10.0		10/ 5	0.25	38/19	6.5
				8/28	6.4	22/11	11.0		10/ 6	66.5	40/20	5.0
9/18	24.0	20/10	11.5						10/ 7	10.0	40/20	6.0
9/20	46.0	22/11	9.9	10/27	15.75	36/18	6.6		10/ 8	3.05	40/20	6.0
9/21	27.0	22/11	10.5	10/28	20.5	38/19	6.0					
				10/29	Incomplete				11/10	25.0	50/25	4.6
10/11	22.0	36/18	6.5	10/30	3.5	40/20	6.0		11/11	5.0	50/25	5.0
10/12	5.0	30/15	8.0	10/31	0	38/19	6.5		11/12	10.0	50/25	4.8
10/13 & 10/14	Incomplete			11/ 1	35.8	40/20	5.5		11/13	Trace	48/24	5.0

10/15	75.8	24/12 + 5	7.0
10/16	92.0	26/13 + 15	5.0
10/17	49.7	28/14 + 10	6.0
10/18	65.0	30/15 + 7	6.0
10/19	12.2	32/16	7.2
10/20	16.0	32/16	7.3
10/21	27.7	32/16	7.0
10/22	62.5	34/17 + 7	5.3
10/23	6.0	34/17	7.0
10/25	79.0	38/19 + 7	4.5
10/26	2.0	36/18	6.8
11/22	13.9	44/22	5.4
11/23	23.7	42/21	5.5
11/24	45.5	44/22	5.0
11/25	6.5	42/21	6.0
11/26	Incomplete	40/20	
11/27	5.5	42/21	6.0
11/28	4.0	44/22	5.5
11/29	41.0	46/23	4.7
11/30	1.0	46/23	5.2
12/ 1	7.7	44/22	5.5
12/ 2	Incomplete	44/22	
12/ 3	54.0	42/21 + 7	4.5 (neck swollen)
12/ 4	13.9	44/22	5.4
1953			
11/ 2	Incomplete		
11/ 3	31.5	42/21 + 5	5.0
11/ 4	39.3	44/22 + 5	4.6 cold
11/ 5	52.8	46/23 + 10	4.0
11/ 6	1.0	46/23	5.3
11/ 8	3.0	48/24	5.0
11/ 9	7.0	48/24	5.0
12/21	1.5	52/26	4.7
12/22	0	50/25	5.0
12/23	2.0	48/24	5.0
12/24	0.5	46/23	5.3
12/25	22.5	46/23	5.0
12/27	17.5	48/24	5.0
12/28	43.0	50/25	4.4
12/29	20.5	52/26	4.5
12/30	16.0	52/26	4.5
12/31	22.5	52/26	4.5
1953			
1/ 1	30.5	52/26	4.4
11/15	5.0	48/24	5.0
11/16	Trace	46/23	5.4
11/17	0	48/24	5.0
11/18	18.7	48/24	5.0
11/19 to 11/21	Incomplete		
12/ 5	53.2	46/23	4.2
12/ 6	52.0	50/25	4.2
12/ 7	12.0	50/25	4.7
12/ 8	Trace	50/25	5.0
12/ 9	6.0	48/24	5.0
12/10	7.0	48/24	5.0
12/11	17.0	48/24	5.0
12/12	0	48/24	5.0
12/13	27.7	48/24	4.7
12/14	14.0	50/25	4.7
12/15	12.5	50/25	4.8
12/16	20.5	52/26	4.5
12/17	4.75	52/26	4.7
12/18	5.0	52/26	4.7
1953			

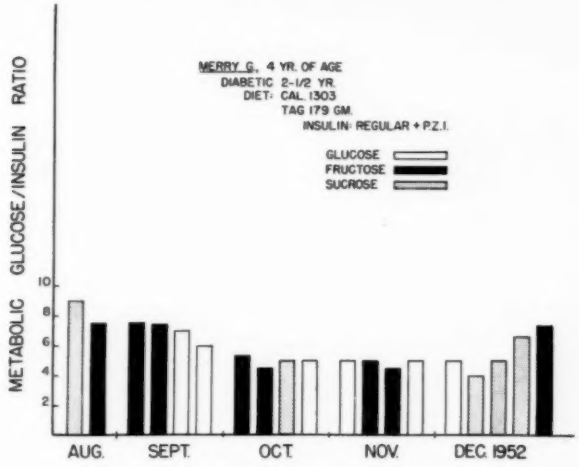
child, developed diabetic symptoms in the fall of 1949 when nearing her tenth birthday. Hospital admission on Dec. 20, 1949, established the diagnosis of diabetes mellitus of considerable severity but without ketosis or acidosis. During the two weeks of hospitalization required for her learning of our control method, her tolerance improved from a G/I ratio of 6 to one of 10. Steady improvement of tolerance with decreasing insulin requirement was then noted, and in March, 1950, she remained completely free of glycosuria for four days after insulin had been discontinued. Secondary loss of tolerance then began and continued with some fluctuation until the early part of 1952 when G/I ratios of 4 and 5 were observed. During this period, however, chronic but active respiratory infection was present, and improvement of tolerance with G/I ratios of 8 to 10 followed recovery from infection just prior to the study period. Her over-all physical progress is shown on her Wetzel Grid (Fig. 5, *B*). At the time of this study, the standard diet called for 2,680 calories and 370 grams total available glucose.

During the first study period, when *sucrose* furnished 25 per cent of the total calories, the daily ratios ranged from 8 to 11, averaging 10.1. Switch to fructose showed ratios ranging from 9.9 to 14.8, and averaging 11.7. Switch to glucose was associated with declining ratios ranging from 4 to 9 and averaging 6.0. Switch back to fructose, however, showed no regaining of tolerance, and the G/I ratios during this period ranged from 4.5 to 8.0 and averaged 6.4. Switches then to sucrose, to glucose, to fructose, to glucose, and finally back to sucrose were accompanied by very little fluctuation in ratio, which slowly declined and stabilized at approximately 5 (Fig. 5, *A*).

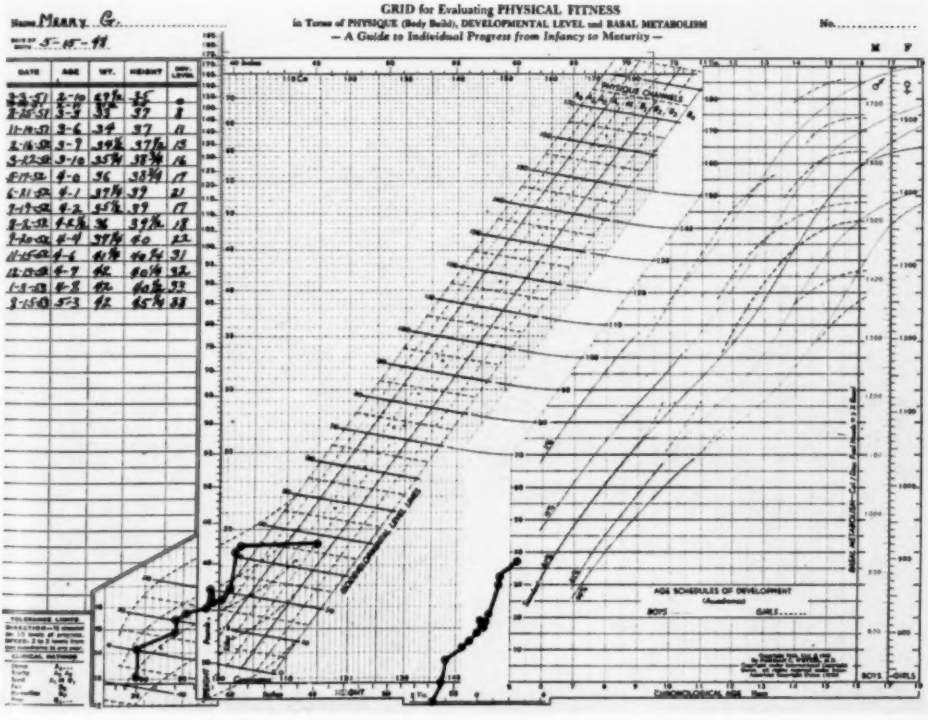
Here, again, except for a very short period during the first fructose diet, there was no suggestion that fructose could be used with a sparing of insulin.

CASE 3.—Merry G. This girl was 4 years old at the time of this study. Her diabetic history was very unusual. She was said to have been in excellent health until 26 months of age when hospital admission in her home town was necessary because of rapid loss of consciousness. Diabetes mellitus was established as present, but some type of encephalopathy was suggested because of continued unconsciousness for the next sixteen days, despite recovery from acidosis and freedom at least from persistent hypoglycemia. At the onset of her illness, a rash thought to resemble chicken pox had been noted, so that when she was transferred to the St. Louis Children's Hospital after the first sixteen days of unconsciousness, we felt that she might be suffering from varicella encephalitis and brain injury the result of frequent hypoglycemic episodes. Complete unconsciousness continued for four more weeks, during which nasal tube feedings were necessary. Examination revealed normal spinal fluid and x-ray of skull but a very abnormal EEG with the predominant pattern of irregular slow 3 to 6 per second activity of rather low voltage. A pneumoencephalogram showed slightly dilated ventricles with more air than normal in the subarachnoid spaces still present in puddles at the end of twenty-four hours. An x-ray diagnosis of cortical atrophy was made.

Slow but steady improvement was noted after the first six weeks of illness, but for a long time mentality remained at a very low level, and behavioral difficulties were severe. Her physical progress was especially good as depicted in her Wetzel Grid (Fig. 6, *B*), and she grew up to be a very attractive child, winning first place in a beauty contest when 2 years 10 months old and only six months after the beginning of her illness. To add to the confusion, she appeared in the outpatient department one day with typical chicken pox! Repeated EEG's showed steady improvement, although a cerebral dysrhythmia remained, and the convulsive tendency, without necessarily a hypoglycemic component, required anticonvulsive medication, phenobarbital, and Dilantin. At the


MERRY G., 4 YR. OF AGE
DIABETIC 2-1/2 YR.
DIET: CAL. 1303
TAG 179 GM.
INSULIN: REGULAR + P.Z.I.
GLUCOSE
FRUCTOSE
SUCROSE
METABOLIC GLUCOSE/INSULIN RATIO
10
8
6
4
2
AUG.
SEPT.
OCT.
NOV.
DEC. 1952

A.


GRID for Evaluating PHYSICAL FITNESS
in Terms of PHYSIQUE (Body Build), DEVELOPMENTAL LEVEL and BASAL METABOLISM
— A Guide to Individual Progress from Infancy to Maturity —
Name MERRY G.
No.
DATE
AGE
WT.
HEIGHT
DEV. LEVEL
PHYSIQUE CHANNELS
AGE SCHEDULES OF DEVELOPMENT
BOYS
GIRLS
CHRONOLOGICAL AGE

B.

Fig. 6.

TABLE III. MERRY G.: AGED 4 YEARS; DIET 1,303 CALORIES; 179 GRAMS TAG; G/I 10 AND 11

FRUCTOSE PERIODS				SUCROSE PERIODS				GLUCOSE PERIODS			
DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/24 HR.	G/I	DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/24 HR.	G/I	DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/ 24 HR.	G/I
1952				*1952*				*1952*			
8/25	18.7	12/ 9	7.7	8/ 7	41.0	8/ 8	12.0	9/12	56.3	11/ 7	7.0
8/26	9.4	11/ 9	8.5	8/ 8	49.5	8/ 8	11.0	9/13	Incomplete		
8/27	29.2	11/ 9	7.5	8/ 8	35-40.0	6/6-12/12	6.0	9/14	35.9	12/ 8	7.0
8/28	44.1	13/ 7	6.7	to				9/15	18.4	12/ 8	8.0
8/29	37.2	13/ 7	7.0	8/16				9/16	41.3	12/ 8	7.0
9/ 1	22.5	13/ 8	7.0	8/16	20-25.0	12/10	7.0	9/17	38.2	13/ 9	6.0
9/ 2	20.5	13/ 8	8.0	to				9/18	Incomplete		
9/ 3	4.6	13/ 8	8.3	8/23				9/19	41.2	13/ 9	6.0
9/ 4	9.0	13/ 8	8.0					9/20	Incomplete	13/ 9	
9/ 5	39.0	13/ 8	6.6	10/11	tr.-2%	21/11		&			
			(cold?)	10/12	12.7	21/11	5.0	9/21			
9/ 7	17.9		8.0	10/13	21.2	21/11	5.0	9/22	44.4	13/ 9	6.0
9/ 8	20.8		7.0	10/14	tr.-4%	21/11		9/23	26.9	16/ 8	6.0
9/ 9	33.4		6.0	10/15	tr.-4%	21/11		9/24	28.4	16/ 8	6.0
9/10	26.4		Convul-	10/16	½-1%	21/11		9/25	8.4	18/ 9	6.0
			sion	10/17	½-4%	21/11					
9/11	19.3		9.0	10/18	2-4%	21/11	Incomplete				
9/12	56.0		7.0	10/19	3-5%	21/11		10/25	Trace	21/11	
				10/20	tr.-4%	21/11		10/26	20.1	21/11	5.0
9/27	21.0	18/ 9	5.0	10/21	½-4%	21/11		10/27	12.2	21/11	6.0
9/28	Incomplete			10/22	1-3%	21/11		10/28	20.0	21/11	5.0
9/29	12.7	18/ 9	6.0	10/23	15.1	21/11	5.0	10/29	2-3%	21/11	
9/30 & 10/ 1	Incomplete	18/ 9		10/24	32.0	21/11	4.0	10/30	30.3	21/11	4.0

10/ 2	21.6	18/ 9	5.0
10/ 3 to 10/ 5	Incomplete		
10/ 6	28.4	22/11	5.0
10/ 7	15.3	22/11	5.0
10/ 8	Incomplete		
10/ 9	37.1	22/11	4.0
10/10	39.3	22/11	4.0
11/ 8	2-3%	22/11	
11/ 9	32.0	22/11	5.0
11/10	59.8	26/13 + 5	3.0 } TAG not accurate;
11/11	17.1	22/11	5.3 } had taken extra food.
11/12	1-4%	22/11	
11/13	23.5	22/11	5.0
11/14	Trace-4%	22/11	
11/15	Trace-2%	22/11	
11/16	16.6	24/12	5.0
11/17	Trace-2%	24/12	
11/18	11.7	24/12	5.0
11/19	12.5	24/12	4.0
11/20	29.8	24/12 + 4	4.0 (Complained of abdominal pain.)
11/21	2-4%	26/13	
12/28	9.1	14/ 7	8.0
12/31	3%	18/ 9	
1953			
1/ 1	20.0	18/ 9	6.0
1/ 2	8.1	18/ 9	6.3
12/ 7	41.7	22/11	4.0
12/ 8	66.8	22/11 + 10	Diarrhea and vomiting
12/ 9	9.5	22/11	
12/10	1-5%	22/11	
12/11	1-6%	22/11 + 5	Diarrhea and vomiting
12/12	21.4	22/11	4.0
12/13	1-2%	22/11	} Diarrhea and vomiting
12/14	1-6%	22/11	
12/15	64.9	22/11 + 10	
12/16	1-3%	22/11	
12/17	8.9	22/11	5.0
12/18	14.5	22/11	5.0
12/19	15.6	22/11	5.0
12/20	1-3%	22/11	
12/21	22.1	22/11	5.0
12/22	7.6	22/11	5.0
12/23	14.7	20/10	5.5
12/24	8.3	18/ 9	8.0
12/25	¼-3%	14/ 7	
12/26	10.4	14/ 7	8.0
12/27 Record lost, spilled heavily, given extra insulin and had reaction during the night			
10/31	1-2%	21/11	
11/ 1	15.2	22/11	5.0
11/ 2	16.5	22/11	5.0
11/ 3	Trace-3%	21/11	
11/ 4	17.0	22/11	5.0
11/ 5	12.6	21/11	5.0
11/ 6	Trace-3%	22/11	
11/ 7	15.6	22/11	5.0
11/22	¼-3%	22/11	
11/23	13.1	22/11	5.0
11/24	23.5	22/11	4.7 } Cold
11/25	2-6%	22/11	} Cold
11/26	20.6	22/11	4.8
11/27	15.6	22/11	5.0
11/28	11.9	22/11	5.0
11/29	1-3%	22/11	
11/30	12.3	22/11	5.0
12/ 1	11.3	22/11	5.0
12/ 2	Trace-3%	22/11	
12/ 3	21.8	22/11	5.0
12/ 4	20.7	22/11	5.0
12/ 5	½-2%	22/11	

age of 3, psychometric and psychologic studies showed her to be only slightly retarded in mental and emotional development.

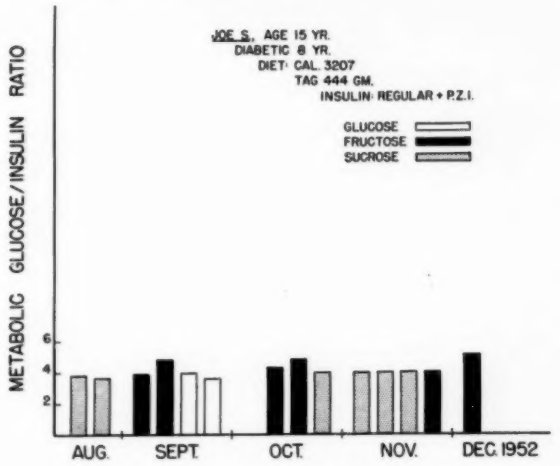
The diabetic progress was that of apparent stability at the 10 to 11 level on the standard diet yielding 1,303 calories and 179 grams total available glucose. Because of the cerebral dysrhythmia with convulsive tendency, glucosuria was permitted to a greater degree than usual in order that hypoglycemia would not confuse the situation. The short period on sucrose was associated with loss of tolerance which was not regained during the subsequent period on fructose. Switches then to glucose, back to fructose, to sucrose, to glucose, to fructose, to glucose, to sucrose, and finally back to fructose showed no significant changes in ratio, although toward the end of the study a period of slight improvement of tolerance was noted. (Fig. 6, *A*.)

Here again insulin requirements were not reduced by utilization of significant amounts of fructose in the diet.

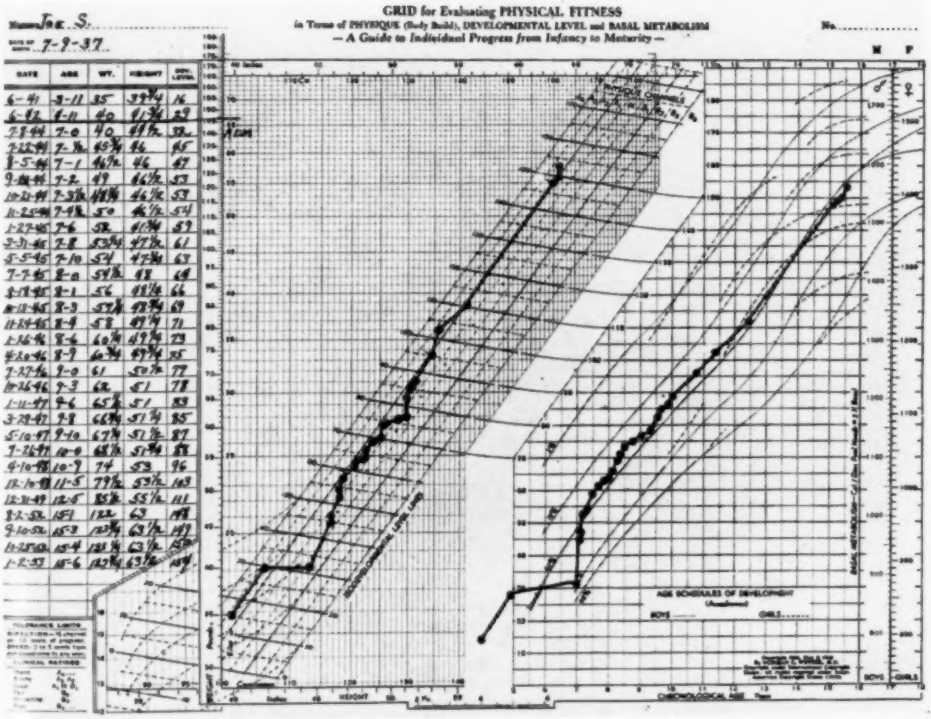
Case 4.—Joe S. This boy was 15 years old when this study was made. His diabetes mellitus began at the age of 7. There was nothing at all unusual about the diabetic course, which was characterized by early recovery of tolerance that allowed him to remain without insulin and without glycosuria after the first two months of regulation. Then secondary loss of tolerance, with some tendency toward remission and exacerbation, was noted with final stability at a level thought consistent with total diabetes. Excellent physical progress is shown by his Wetzel Grid (Fig. 7, *B*).

Prior to these studies he was on a standard diet of 3,207 calories with 444 grams of available glucose and had shown stability with good regulation at the low ratios of 3 to 3.8. No change in ratio followed the sucrose diet. Switches to fructose, to glucose, back to fructose, to sucrose, and back to fructose showed no consistent change in ratio and very little fluctuation. Because of the very great severity of this boy's diabetes, the substitution of fructose for glucose theoretically might have spared 50 units of insulin and raised the G/I ratio from 4 to 8, and the use of sucrose, 25 units, with improvement of G/I ratio from 4 to 6. So here again no insulin-sparing effect by fructose could be demonstrated. (Fig. 7, *A*.)

Case 5.—Donna W. This girl developed the first signs of diabetes mellitus at the age of 2½ years, and diagnosis was made when she was admitted to the hospital two weeks later with severe acidosis and in coma on Oct. 31, 1949. Her subsequent diabetic course was that of initial amelioration of severity which allowed her to be without insulin for several weeks in December, 1949, without glycosuria. Secondary loss of tolerance then was noted with more than the usual degree of remission and exacerbation because of frequent respiratory infections. Her physical progress, however, was good (Fig. 8, *B*). At the time of this study, although this 6-year-old child had had diabetes for three and a half years, she was the least severe of the group. On the standard diet yielding 1,878 calories and 263 grams total available glucose, G/I ratios of 12 to 16 were noted. Study started with the fructose diet, and almost immediately improvement of tolerance followed with reduction of insulin dosage to one-half the usual and a doubling of the G/I ratio from 12.8 to 25.9. Toward the end of the period, however, some loss of tolerance occurred which continued slowly throughout the following glucose diet and the first week of the subsequent fructose diet, at the end of which the G/I ratio was 11.0. With continuation of the fructose diet, there was noted improved tolerance for a while and then again later loss throughout the following glucose period. It was perhaps significant that the gain in tolerance on the fructose periods was not im-


JOE S. AGE 15 YR.
DIABETIC 8 YR.
DIET: CAL. 3207
TAG 444 GM.
INSULIN: REGULAR + P.Z.I.
GLUCOSE
FRUCTOSE
SUCROSE
METABOLIC GLUCOSE/INSULIN RATIO
6
4
2
AUG.
SEPT.
OCT.
NOV.
DEC. 1952

A.


GRID for Evaluating PHYSICAL FITNESS
in Terms of PHYSIQUE (Body Build), DEVELOPMENTAL LEVEL and BASAL METABOLISM
— A Guide to Individual Progress from Infancy to Maturity —
Name Joe S.
Date 7-9-37
No.
DATE
AGE
WT.
HEIGHT
DEV. LEVEL
6-41 8-11 35 39¾ 16
6-42 9-11 40 41¾ 29
7-3-43 10-0 40 41½ 32
2-22-44 10-7½ 45¾ 46 45
8-5-44 11-1 46½ 46 47
9-24-44 11-2 49 46½ 53
10-21-44 11-3½ 48¾ 46½ 53
11-25-44 11-4½ 50 46½ 54
1-27-45 11-6 52 47¼ 59
2-21-45 11-8 53¾ 47½ 61
5-5-45 11-10 54¼ 47¾ 63
7-7-45 12-0 54½ 48 64
8-13-45 12-1 56 48½ 66
10-12-45 12-3 57½ 48¾ 69
11-29-45 12-4 58 49¼ 71
1-16-46 12-6 60¾ 49½ 73
4-26-46 12-9 60¾ 49¾ 75
7-27-46 13-0 61 50¼ 77
10-26-46 13-3 62 51 78
1-11-47 13-6 65½ 51 83
3-28-47 13-8 66¾ 51¼ 85
5-10-47 13-10 67¾ 51½ 87
7-26-47 14-0 68½ 51¾ 88
9-10-47 14-2 74 52¾ 96
12-10-47 14-5 77½ 53½ 103
12-31-47 14-5 85½ 55½ 111
3-2-48 15-1 122 63 148
9-10-48 15-3 123¾ 63½ 149
11-25-48 15-4 123½ 63½ 150
1-2-49 15-6 123¾ 63½ 149
AGE SCHEDULES OF DEVELOPMENT
(Anesthesia)
BOYS
GIRLS
CHRONOLOGICAL AGE
HEIGHT

B.

Fig. 7.

TABLE IV. JOE S.: AGED 15 YEARS; DIET 3,207 CALORIES; 444 GRAMS TAG; G/I 3 TO 3.8

FRUCTOSE PERIODS				SUCROSE PERIODS				GLUCOSE PERIODS			
DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/24 HR.	G/I	DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/24 HR.	G/I	DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/24 HR.	G/I
1952				*1952*				*1952*			
9/ 7	19.9	78/39	3.6	8/16 to 8/23	50-30	68/34-74/37	3.7-3.9	9/22	1-3%	60/30	
9/ 8	½-1%	76/38						9/23	1-3%	62/31	
9/ 9	½-1%	74/37	Incomplete, in school	8/23 to 9/ 1	23-25	74/37-76/38	3.7-3.8	9/24	1-3%	64/32	Incomplete, in school
9/10	1-3%	74/37						9/25	1-3%	66/33	
9/11	1-3%	72/36		9/ 1 to 9/ 5	Incomplete	78/39		9/26	1-3%	66/33	
9/12	1-3%	72/36						9/28	16.4	70/35	4.0
9/13	7.4	70/35	4.0					9/29	18.6	72/36	4.0
9/14	8.4	68/34	4.0	10/20	1%	62/31		9/30	½-3%	74/37	
9/15	1-3%	68/34		10/21	½-1%	64/32	Incomplete	10/ 1	½-3%	78/39	Incomplete, in school
9/16	0-1%	66/33	Incomplete, in school	10/22	½-3%	66/33		10/ 2	½-3%	80/40	
9/17	1-3%	64/32		10/23	10.8	68/34	4.2	10/ 3	½-3%	80/40	
9/18	1%	62/31		10/24	½-3%	70/35	(Incomplete)	10/ 4	18.0	80/40	3.6
9/19	0-1%	62/31		10/25	8.8	72/36	4.0	10/ 5	26.0	80/40	3.6
9/20	8.8	60/30	4.8	10/26	5.6	74/37	4.0				
9/21	8.8	60/30	4.8	10/27	½-1%	76/38					
				10/28	½-1%	76/38	(Cold)				
10/ 6	½-1%	76/38		10/29	14.6	78/39	4.0				
10/ 7	1%	74/37		10/30	½-1%	80/40					
10/ 8	0-1%	72/36	Incomplete, in school	10/31	½-1%	80/40					
10/ 9	½-1%	70/35		11/ 1	0-1%	80/40					
10/10	½-1%	70/35		11/ 2	13.2	80/40	4.0				

10/11	7.0	68/34	4.2	11/ 3	3-1%	80/40				
10/12	11.0	66/33	4.5	11/ 4	0-5%	82/41 + 10	(Nauseated)			
10/13	0-3%	64/32		11/ 5	6.6	80/40	4.0			
10/14	3-1%	62/31	Incomplete, in school	11/ 6	3-1%	80/40				
10/15	1-3%	60/30		11/ 7	3-1%	80/40				
10/16	3-3%	60/30		11/ 8	4.0	80/40	4.0			
10/17	1-3%	60/30		11/ 9	6.9	80/40	4.0			
10/18	8.2	60/30	4.8	11/10	3-1%	80/40				
10/19	9.3	60/30	4.8	11/11	0-1%	80/40				
				11/12	1%	80/40				
11/22	3-1%	80/40		11/13	0-1%	80/40				
11/23	13.8	78/39	3.7	11/14	3-1%	80/40				
11/24	3-1%	76/38		11/15	0-1%	80/40				
11/25	3-1%	74/37		11/16	8.6	80/40	4.0			
11/26	3-1%	72/36		11/17	3-1%	80/40				
11/27	3-1%	70/35		11/18	3-1%	80/40				
11/28	3-1%	68/34		11/19	3-1%	80/40				
11/29	14.6	66/33	4.3	11/20	0-1%	80/40				
11/30	6.4	64/32	4.5							
12/ 1	3-1%	62/31								
12/ 2	0-1%	60/30								
12/ 3	0-1%	60/30								
12/ 4	0-1%	56/28								
12/ 5	3-1%	54/27								
12/ 6	0-1%	52/26								
12/ 7	5.5	50/25	5.8							

TABLE V. DONNA W.: AGED 2½ YEARS; DIET 1,878 CALORIES; 263 GRAMS TAG; G/I 12 TO 16

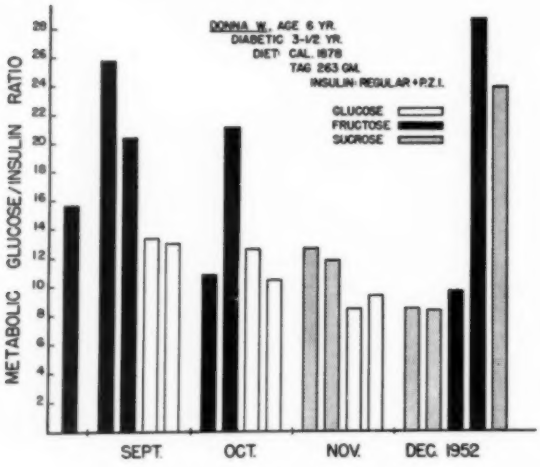
FRUCTOSE PERIODS				SUCROSE PERIODS				GLUCOSE PERIODS			
DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/ 24 HR.	G/I	DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/ 24 HR.	G/I	DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/ 24 HR.	G/I
1952				*1952*				*1952*			
8/24	6.56	10/10	12.8	11/ 2	12.4	12/12	10.4	9/14	21.35	8/ 8	15.0
8/25	7.0	8/ 8	16.0	11/ 3	21.15	12/12	10.0	9/15	18.2	9/ 9	13.6
8/26	19.3	7/ 7	17.4	11/ 4	10.2	13/13	9.7	9/16	27.6	9/ 9	13.0
8/27	15.3	8/ 8	15.5	11/ 5	11.7	11/11	11.4	9/17	25.4	10/10	11.9
8/28	3.05	8/ 8	16.2	11/ 6	21.1	11/11	11.0	9/18	13.1	10/10	12.5
8/31	3.75	5/ 5	25.9	11/ 7	14.9	11/11	11.2	9/19	20.3	9/ 9	13.5
9/ 1	7.5	5/ 5	25.5	11/ 8	12.7	10/10	12.5	9/21	13.6	9/ 9	13.8
9/ 2	7.5	5/ 5	25.5	11/ 9	15.5	10/10	12.3	9/22	14.6	10/10	12.8
9/ 3	0	5/ 5	26.3					9/23	16.6	9/ 9	13.6 ? Incomplete in kindergarten
9/ 4	1.0	5/ 5	26.2	Refused part				9/24	8.4	9/ 9	14.1
9/ 5	6.0	5/ 5	25.6	of TAG				9/25	26.4	10/10	11.8
9/ 7	17.9	6/ 6	20.4					9/26	21.0	11/11	11.0
9/ 8	9.8	7/ 7	18.0	11/10	15.0	11/11	11.4				
9/ 9	10.5	6/ 6	21.0	11/11	13.75	11/11	11.3	10/21	11.25	9/ 9	13.9
9/10	4.3	6/ 6	21.5	11/12	15.4	10/10	12.4	10/22	14.4	9/ 9	13.2
9/11	Refused food and vomited			11/13	18.75	10/10	12.2	10/23	15.5	9/ 9	13.7
9/12	11.8	6/ 6	20.9	11/14	15.0	11/11	11.2	10/24	17.4	10/10	12.2
								10/25	13.2	11/11	11.3
9/28	Incomplete	10/10		11/30	7.0	15/15	8.5	10/26	12.35	11/11	11.3
9/29	8.5	10/10	12.7	12/ 1	7.75	14/14	9.0	10/27	14.25	12/12	10.3
9/30	20.6	10/10	12.0	12/ 2	11.75	15/15	8.3	10/28	15.9	12/12	10.2
10/ 1	25.6	11/11	10.8	12/ 3	7.35	15/15	8.4	10/29	15.0	12/12	10.3
10/ 2	8.9	12/12	10.6	12/ 4	8.5	14/14	9.0	10/30	12.45	12/12	10.4
10/ 3	57.0	12/12	8.9	12/ 5	13.4	15/15	8.3	10/31	10.2	11/11	11.5
10/ 5	10.4	12/12	10.5								
10/ 6	18.9	11/11	11.0	May have been				11/16	11.2	13/13	9.0
10/ 7	2.9	11/11	11.8	incomplete				11/17	7.5	14/14	9.3
10/ 8	4.3	10/10	12.9					11/18	13.2	15/15	8.3
10/ 9	3.0	8/ 8	16.2	Slight reaction				11/19	5.5	16/16	8.0
10/10	0	7/ 7	18.7?	Incomplete				11/20	3.0	16/16	8.1
10/12	5.7	6/ 6	21.4					11/21	4.2	15/15	8.6
10/13	1.7	5/ 5	26.1	12/ 6	6.25	14/14	9.0	11/22	1.7	15/15	8.6
10/14	11.55	5/ 5	25.1	12/ 7	12.9	15/15	8.3	11/23	2.4	13/13	10.0
10/15	5.0	6/ 6	21.5	12/ 8	11.0	16/16	7.8	11/24	8.7	13/13	9.7
10/16	4.5	6/ 6	21.5	12/ 9	9.0	15/15	8.5	11/25	5.5	13/13	9.8
10/17	11.5	5/ 5	25.1	12/10	9.2	14/14	9.0	11/26	8.4	13/13	9.8

10/19	16.3	8/ 8	15.4	12/11	4.25	15/15	8.6	11/27	15.6	14/14	8.8
10/20	15.2	9/ 9	14.9	12/12	19.9	15/15	8.0	11/28	5.2	15/15	8.6
12/14	16.3	16/16	7.7	12/26	23.8	4/ 4	30.0	*1953*			
12/15	3.7	16/16	8.0	12/27	19.15	5/ 5	24.4				
12/16	4.65	14/14	9.2	12/28		4/ 4	} Fever; did not				
12/17	6.45	13/13	9.8	12/29	17.9	3/ 3	} get TAG				
12/18	3.2	12/12	10.8	12/30	48.0	5/ 5	21.5	2/ 8	9.9	12/12	10.5
12/19	9.6	10/10	12.6	12/31	21.35	6/ 6	20.1	2/ 9	6.05	13/13	9.8
12/21	3.75	7/ 7	18.5	*1953*				2/10	10.9	13/13	9.8
12/22	5.75	6/ 6	21.5	1/ 1	27.8	7/ 7	16.5	2/11	5.35	14/14	9.1
12/23	1.75	5/ 5	26.1	1/ 2	28.9	9/ 9	13.0	2/12	7.05	12/12	10.6
12/24	2.75	4/ 4	32.5	1/ 3	22.3	11/11	11.0	2/13	10.15	12/12	10.5
12/25	7.0	3/ 3	42.6	1/ 4	21.1	13/13	9.3	2/14	21.7	13/13	9.2 Earache
				1/ 5	16.6	15/15	8.2	2/15			
1953				1/ 6	13.1	17/17	7.3	to	Refused food; TAG unknown		
				1/ 7	3.75	19/19	6.7	2/20			
1/11	7.5	15/15	8.5	1/ 8	5.35	17/17	7.6				
1/12	5.5	13/13	9.9	1/ 9	9.55	15/15	8.4	3/22	12.55	10/10	12.5
1/13	5.8	11/11	11.8					3/23	9.4	12/12	10.5
1/14	3.45	9/ 9	14.4	2/22	15.2	13/13	9.5	3/24	9.75	12/12	10.5
1/15	20.4	8/ 8	15.0	2/23	17.5	14/14	8.8	3/25	11.0	12/12	12.5
1/16				2/24	17.7	15/15	8.2	3/26	11.0	13/13	9.3
to	"Flu," did not take TAG			2/25	21.0	16/16	7.5	3/27	8.3	14/14	9.1
1/23				2/26	12.5+	18/18		3/28	12.9	14/14	8.9
1/25	3.7	8/ 8	16.0	2/27	8.0+	16/16	Slight reaction				
1/26	9.9	6/ 6	21.0	3/ 1	15.9	17/17	7.2	3/29	7.95	15/15	8.5
1/27	14.7	8/ 8	15.5	3/ 2	6.25	17/17	7.5	3/30	5.2	14/14	9.2
1/28	21.7	10/10	12.0	3/ 3	9.1	17/17	7.4	3/31	9.2	13/13	9.7
1/29	9.65	12/12	10.5	3/ 4	7.65	18/18	7.0	4/ 1	5.65	13/13	9.5
1/30	22.5	13/13	9.2 (Otitis)					4/ 2	8.5	12/12	10.5
1/31	11.6	12/12	10.4	3/ 5	5.1	16/16	8.0	4/ 3	13.4	12/12	10.4
2/ 1	7.4	11/11	11.6	3/ 6	13.9	17/17	7.3				
2/ 2	6.8	10/10	12.5	3/ 7	11.45	18/18	6.9	6/14	22.8	15/15	8.0
2/ 3	10.4	11/11	11.4					6/15	26.8	16/16	7.3
2/ 4	13.3	12/12	10.0	4/19	20.1	13/13	9.3	6/16	19.3	17/17	7.1
2/ 5	6.1	13/13	10.0	4/20	17.2	15/15	8.2	6/17	14.2	18/18	6.9
2/ 6	7.2	12/12	10.6	4/21	16.6	16/16	7.6	6/18	16.6	18/18	6.8
				4/22	12.6	16/16	7.8	6/19	7.16	19/19	6.7
3/ 8	9.1	18/18	7.3	4/23	15.75	17/17	7.2				
3/ 9	6.85	16/16	8.0	4/24	23.3	18/18	6.6	6/28	15.5	10/10	12.3
3/10	6.5	14/14	9.1	4/25	13.2	20/20	6.2	6/29	16.9	10/10	12.3
3/11	3.95	12/12	10.7	4/26	10.8	20/20	6.3	6/30	4.45	12/12	10.7
3/12	5.6	10/10	12.3	4/27	2.15	18/18	7.2	7/ 1	12.5	10/10	12.5

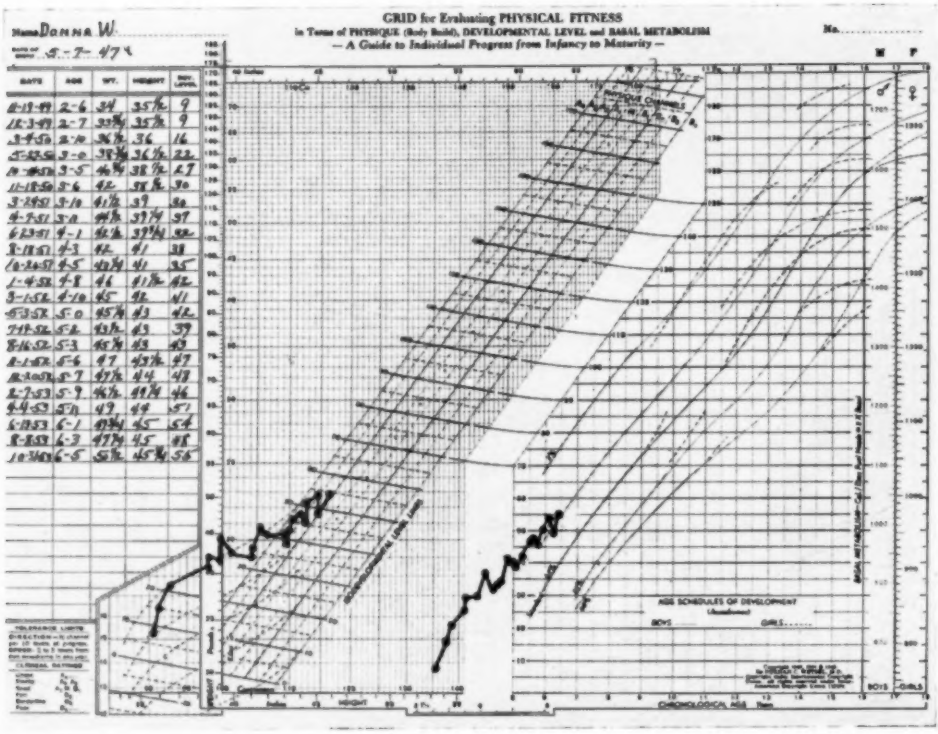
TABLE V. CONT'D

FRUCTOSE PERIODS				SUCROSE PERIODS				GLUCOSE PERIODS			
DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/ 24 HR.	G/I	DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/ 24 HR.	G/I	DATE	URINE GLUC. GM./24 HR. OR PER CENT	INSULIN (MIXED REG. + PZI) UNITS/ 24 HR.	G/I
3/13	11.85	8/ 8	15.6	4/28	8.4	16/16	7.3	7/ 2	15.8	10/10	12.3
3/14	15.15	8/ 8	15.5	4/29	13.5	15/15	8.3	7/ 3	21.65	11/11	10.9
3/15	7.0	10/10	12.5	5/ 1	15.7	14/14	8.8	7/ 6	26.8	12/12	9.7
3/16	4.8	10/10	12.9	5/ 2	Ate unknown quantity of food and sweets—vomiting and acidosis; admitted to hospital			7/ 7	9.6	14/14	9.0
3/17	11.05	8/ 8	15.7					7/ 9	14.8	10/10	12.4
3/18	14.25	10/10	12.4					7/10	5.9	8/12	12.8
3/19	5.0	12/12	10.7	5/ 7	16.2	15/15	8.2	7/11	14.75	6/10	15.5
3/20	0	10/10	Refused TAG								
3/21	15.95	8/ 8	15.3	5/ 8	6.45	13/13	9.8	9/ 6	4.7	10/10	12.9
				5/ 9	15.75	12/13	10.2	9/12	15.0	12/12	10.3
4/ 5	8.75	12/12	10.5	5/10	24.9	14/14	8.5	9/13	17.5	13/13	9.4
4/ 6	13.6	12/12	10.3	5/11	5.6	16/16	8.0				
4/ 7	5.8	13/13	10.7	5/12	12.8	14/14	8.8				
4/ 8	3.25	12/12	10.4	Slight reaction							
4/ 9	7.1	10/10	12.8	5/14	33.0	17/17	6.7				
4/10	17.1	8/ 8	15.3	5/15	8.3	19/19	6.7				
4/11	8.4	10/10	12.7	5/16	23.0	19/19	6.2				
4/12	14.4	10/10	12.4								
4/13	6.7	12/12	10.6	5/29	Incomplete	9/ 9					
4/14	10.7	10/10	12.6	5/30	Incomplete	10/10	Insulin reaction				
4/15	3.45	10/10	13.0	5/31	12.0	8/ 8	15.6				
4/16	5.75	10/10	12.8	6/ 1	14.6	10/10					
4/17	23.1	11/11	12.4	6/ 2	9.5	12/12	10.5				
4/18	8.65	13/13	10.3	6/ 3	21.0	14/14	8.5				
				6/ 4	5.1	16/16	8.0				
5/17	8.3	19/19	6.6	6/ 5	5.4	15/15	8.6				
5/18	2.8	17/17	7.6	6/ 6	7.3	15/15	8.5				
5/19	10.76	15/15	8.4	6/ 7	8.4	15/15	8.5				
5/20	13.9	17/17	7.2	6/ 8	12.8	15/15	8.3				
5/21	5.7	15/15	8.5	6/ 9	9.1	14/14	9.0				
5/22	34.0	15/15	Ate extra food								
5/23	Incomplete			6/10	10.4	14/14	9.0				
5/24	3.6	15/15	8.6	6/11	12.4	15/15	8.4				
5/25	5.0	13/13	9.9	6/12	8.6	15/15	8.5				
5/26	6.9	13/13	9.8	Laceration of head							
5/27	7.2	13/13	9.8								
5/28	3.5	11/11	11.7	6/20	8.6+	17/17	Incomplete				
				6/21 to 6/25	Incomplete						
7/26	8.3	10/10	12.7								

7/27	7.5+	8/ 8	Incomplete	6/26	7.4	10/10	12.8	
7/28	12.8	6/ 6	20.8	6/27	17.1	9/ 9	13.6	
7/29	16.9+	6/ 6	Incomplete	7/12	4.2	8/12	12.9	
7/30	8.8	8/ 8	15.7	7/13	15.3	6/10	15.5	
7/31	12.7	8/ 8	15.6	7/14	8.8	8/12	12.7	
8/ 1	Incomplete	8/ 8		7/15	17.0	8/12	12.3	
8/ 2	12.9	8/ 8	15.6	7/16	12.6	10/14	10.4	
8/ 3	7.2	8/ 8	15.3	7/17	18.8	12/16	8.7	
8/ 4	10.8	6/ 6	20.0	7/19	5.3	10/12	11.7	
8/ 5	8.5	6/ 6	21.1	7/20	13.8	10/10	12.4	
8/ 6	8.3	7/ 7	18.2	7/21	10.2	10/10	12.6	
8/ 7	22.3	6/ 6	20.0	7/22	13.3	10/10	12.5	
8/ 9	5.3	10/10	12.4	7/23	12.1	10/10	12.5	
8/10	12.5	10/10	12.5	7/24	8.8	10/10	12.7	
8/11	13.1	10/10	12.5	7/25	16.4	8/ 8	15.4	
8/12	4.2	11/11	11.7					
8/13	4.8	9/ 9	14.3	8/23	20.5	8/ 8	15.1	
8/14	12.5	8/ 8	15.6	8/24	18.7	10/10	12.2	
8/15	9.5	8/ 8	15.8	8/25	17.3	12/12	10.2	
8/16	12.0	8/ 8	15.6	8/26	11.6	14/14	10.4	
8/17	13.3	8/ 8	15.6	8/27	11.0	14/14	9.0	
8/18	7.1	8/ 8	16.0	8/28	9.0	14/14	9.0	
8/19	21.0	7/ 7	17.2	8/29	17.2	12/12	10.2	
8/20	7.5	9/ 9	14.1	8/30	Incomplete	13/13		
8/21	Incomplete	8/ 8		8/31	8.1	13/13	9.8	
8/22	21.3	6/ 6	20.1	9/ 1	33.2	11/11	10.4	(Probably got extra food)
				9/ 2	8.8	13/13	9.7	
9/20	6.0	10/10	12.8	9/ 3	11.4	13/13	9.6	
9/26	20.5	12/12	10.1	9/ 4	3.6	12/12	10.7	
9/27	15.9	14/14	(Sore throat;					
9/28	17.25	14/14	TAG incomplete					
9/29	8.4	15/15	8.5					
10/ 4	27.0	10/10	11.8	10/18	20.7	10/10	12.1	
10/ 5	11.1	12/12	Incomplete	10/19 to 10/22	Incomplete			
10/ 6 to 10/ 9	Incomplete			10/23	10.3	15/15	8.4	
				10/24	13.4	15/15	8.3	
10/10	11.2	12/12	10.4	10/25	14.1	15/15	8.3	
10/11	6.1	12/12	10.7	10/26	11.7	16/16	7.8	
10/12 to 10/16	Incomplete			10/27 to 10/30	11.6 Incomplete	16/16	7.8	
10/17	12.65	9/ 9	13.3					


DONNA W. AGE 6 YR.
DIABETIC 3-1/2 YR.
DIET CAL. 1878
TAG 263 GM.
INSULIN: REGULAR + P.Z.I.
GLUCOSE
FRUCTOSE
SUCROSE
METABOLIC GLUCOSE/INSULIN RATIO
SEPT.
OCT.
NOV.
DEC. 1952

A.


GRID for Evaluating PHYSICAL FITNESS
in Terms of PHYSIQUE (Body Build), DEVELOPMENTAL LEVEL and BASAL METABOLISM
— A Guide to Individual Progress from Infancy to Maturity —
Name DONNA W.
No.
AGE SCHEDULES OF DEVELOPMENT
BOYS
GIRLS
CHRONOLOGICAL AGE Years

B.

Fig. 8.

mediate but delayed and quite gradual. Switch from the second glucose period to sucrose was without change. Switch back then to glucose was with slight loss of tolerance not regained by switch back again to sucrose. But the best day was 42.6. Switch to a sucrose diet was attended by loss of tolerance again, with final ratios of about 9. Resumption of a fructose diet for now the fourth time was accompanied by only a slight and short

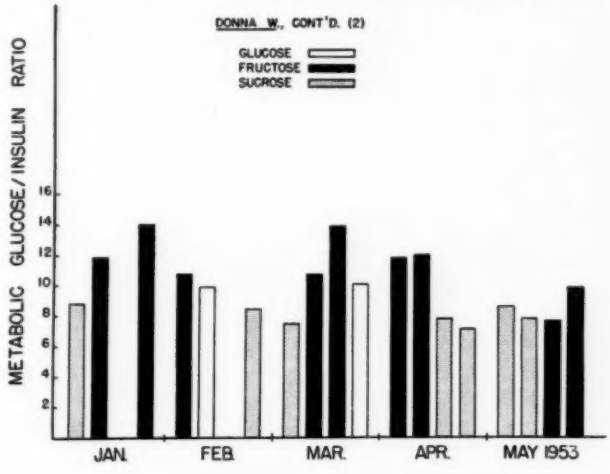


Fig. 9.

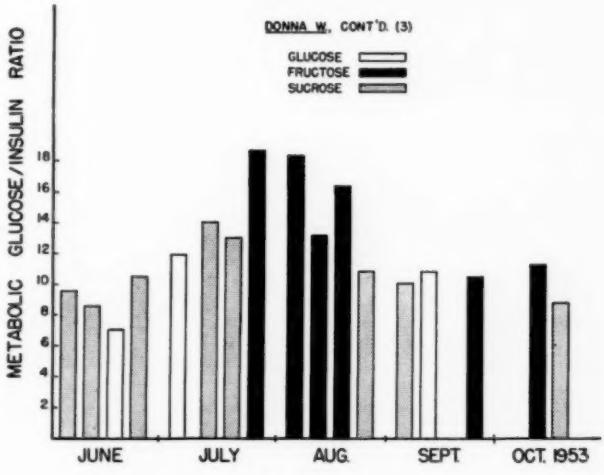


Fig. 10.

change to the third period of fructose diet again showed gain in tolerance, this time leading to a short period during which only 6 units of insulin daily were required. The G/I ratio on improvement. Subsequent switches to glucose, to sucrose, back to fructose, to glucose, to fructose, to sucrose, to fructose, to sucrose, to glucose, to sucrose, to fructose, to sucrose, to

glucose, to fructose, and finally to sucrose showed much less change and were much less suggestive of improvement during the fructose diet periods. (Figs. 8,.1, 9, 10.)

The over-all impression which we gained from this child was that we were seeing spontaneous gains and losses of tolerance, the results of recurring respiratory infections, until finally the losses prevailed with ultimate stabilization at the usual low G/I ratio. It seems worthy of emphasis, however, that gains of tolerance occurred during the fructose periods, the explanation for which is not apparent at this time. The findings suggest that it might be of interest next to study the effects of fructose in earlier and milder cases, still capable of significant degrees and longer periods of recovery of tolerance.

SUMMARY AND CONCLUSIONS

In order to determine whether fructose feeding would influence insulin requirement in diabetes mellitus, five children with severe diabetes were studied in regard to insulin need under three interchangeable arrangements which caused the diet to vary from a standard one to (1) one which permitted *fructose* to furnish 25 per cent of the total calories, (2) *sucrose* to be substituted in equal amounts for fructose, and (3) glucose to be similarly substituted.

In four of the children, despite the varying diets, insulin dosage remained constant, and in them it was concluded that fructose exerted no insulin-sparing effect. In the fifth child, what at first seemed to be an insulin sparing effect, was eventually interpreted as spontaneous improvement of tolerance often seen in the earlier stages of juvenile diabetes mellitus.

MUSCULOSKELETAL DISORDERS SIMULATING POLIOMYELITIS

EUGENE MOSKOWITZ, M.D.
MOUNT VERNON, N. Y.

THE seasonal incidence of anterior poliomyelitis coupled with a tremendous amount of publicity, both in lay and medical circles, has often placed the medical profession in the anomalous position of classifying every disorder of the musculoskeletal system as a potential case of poliomyelitis—particularly if there is an associated febrile illness. During the winter months the situation reverts to normal, so to speak, and a disability is diagnosed on the basis of clinical findings supported by whatever laboratory data are necessary without being under pressure to confirm or rule out a specific disease entity, namely, poliomyelitis.

The problem is particularly difficult when children are involved, where one has to "defer" to the diagnosis of poliomyelitis once the parents have raised the possibility. The history is often unreliable and it is difficult, at times, to establish a causal relationship between the constitutional manifestations, if present, and the local findings. Apprehension on the part of the parents and anxiety on the part of the physician, often fully justified, may lead to premature hospitalization without the customary careful evaluation of the clinical findings. Once the child is in a poliomyelitis ward, the major emphasis is on confirming a specific diagnosis, poliomyelitis, rather than on an "unprejudiced" diagnostic work-up.

The following case histories are presented to illustrate the problem. They have the following factors in common—a seasonal incidence in a geographic area where poliomyelitis was prevalent and where the population and medical profession was "polio conscious," coincidental constitutional manifestations, and localized musculoskeletal symptoms and signs. A diagnosis of poliomyelitis was considered tentatively in all the cases.

CASE REPORTS

CASE 1.—A boy, aged 10 years, complained of severe backache preceded by fever and headache. The child presented the classical "tripod sign" associated with severe spasm of the spine extensor muscles. There was no muscle weakness. Pain was not relieved by local heat applications. X-rays of the dorsolumbar spine revealed extensive osteoporosis with collapse of the vertebral bodies and widening of the intervertebral spaces. Further studies at Babies Hospital (service of Dr. Caffey) confirmed presumptive diagnosis of leukemia, in an aleukemic phase with extensive skeletal involvement. (Fig. 1.)

CASE 2.—A boy, aged 12 years, a typical mongoloid, complained of severe pain in the left thigh radiating to the knee with hamstring spasm and a pronounced limp. Previously he had had a mild upper respiratory infection. There was considerable spasm in the left hip with marked limitation

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of internal rotation and abduction. There was no muscle weakness. X-rays of the left hip revealed a transcervical fracture of the femur with impaction suggestive of an insufficiency fracture. (Fig. 2.)

CASE 3.—A boy, aged 5 years, complained of muscle pain associated with stiffness. The symptoms were preceded for several days by a low-grade fever. There was a questionable history of trauma. He presented marked limitation of flexion and rotation of the cervical spine and would not sit up. X-rays of the cervical spine revealed a minimal subluxation of C_2 on C_3. (Fig. 3.) The neck spasm subsided after twenty-four hours of bed rest. There was no muscle weakness noted.

CASE 4.—A girl, aged 10 years, had a rather sudden onset of pain in the left leg without any trauma. The pain was preceded for several days by upper respiratory manifestations. She walked with a mild limp. External rotation in the left hip was restricted and painful. There was a mild atrophy of the thigh without any muscle weakness. X-rays of the left hip revealed an early epiphyseal separation (slipping).

CASE 5.—A boy, aged 8 years, had awakened with pain in the right leg. There had been no injury. The pain was preceded for several days by m a l a i s e. There were questionable gastrointestinal manifestations. The diagnosis was poliomyelitis and the child was treated at home with hot packs and bed rest by the family physician. He remained inactive for several weeks following which he was ambulated. Subsequently, a progres-

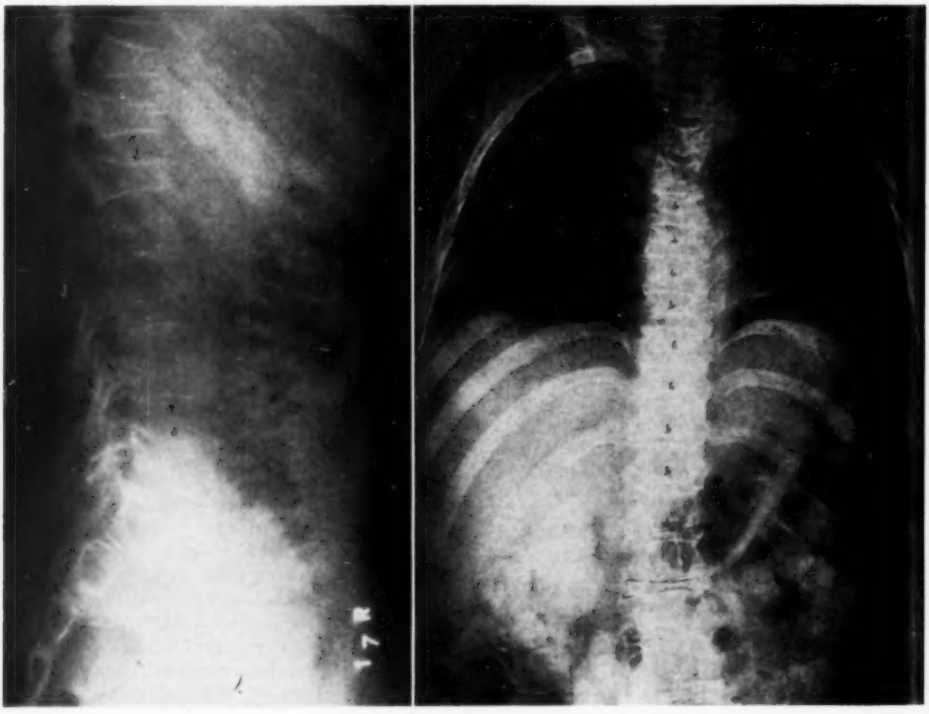

Fig. 1.—Case 1. Leukemia with skeletal involvement. (Courtesy Dr. J. Caffey.)

sive limp was noted. On initial examination, he presented a positive Trendelenburg on testing the right hip and walked with a marked limp. Internal rotation was somewhat restricted. There was generalized atrophy of the entire right leg with a ½ inch shortening. However, there was no weakness in any specific muscle group. X-rays of the right hip revealed an early aseptic necrosis of the femoral head (Perthes') with slight broadening of the femoral neck and minimal fragmentation of the head (Fig. 4). The diagnosis, questioned initially, was subsequently confirmed by films taken at a later date, showing definite progression of the destructive changes. (Fig. 5.)

Fig. 2.—Case 2. Fracture of neck of femur.

CASE 6.—A boy, aged 6 years, had pain and weakness of the right arm,

Fig. 3.—Case 3. Subluxation of C_2–C_3.

Fig. 4.

Fig. 5.

Figs. 4 and 5.—Case 5. Perthes' disease of right hip.

of three weeks' duration, associated with malaise and lethargy. The child was hospitalized at Grasslands Hospital, Valhalla, N. Y. On admission there was some hamstring spasm noted bilaterally. He had rather diffuse weakness in the right upper extremity. Spinal tap was negative. The paresis improved considerably over a period of two weeks. However, he developed severe neck spasm and pain followed by neurological changes suggesting a cervical cord lesion, including areflexia in the upper extremities and clonus and bilateral Babinski signs in the lower extremities. He then developed a quadraparesis. X-rays of the cervical spine revealed destructive changes in the lateral mass of the sixth cervical vertebra on the right, extending into the spinous process but not involving the vertebral body (Fig. 6). Exploratory surgery performed by Dr. Wingebach revealed an invading lesion with pathological diagnosis of Ewing's sarcoma or neuroblastoma. The hamstring "spasm" was due to meningeal irritation and increased with progression of the disease.

CASE 7.—A girl, aged 11 years, had severe pain in the anterior and posterior neck associated with inability to flex the head against gravity. There was a low-grade fever for several days with upper respiratory manifestations. The child was unable to sit up because of severe pain and the neck was splinted in extension. There was no muscle weakness. X-rays of the chest and sternum revealed a generalized osteoporosis of the manubrium suggestive of an early aseptic necrosis. The patient had been playing a large-sized accordion for some time and was accustomed to balancing the upper end of the instrument against the upper chest wall. All the symptoms subsided after a few days' rest and local heat applications.

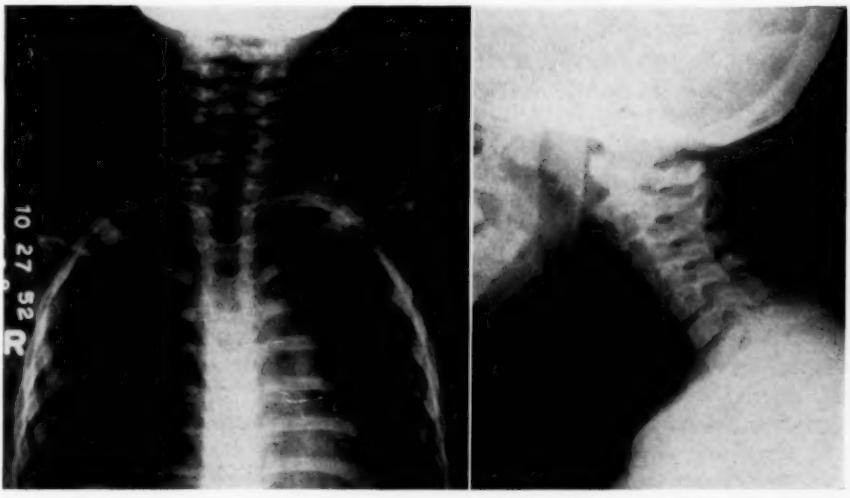

Fig. 6.—Case 6. Sarcoma involving cervical spine.

DISCUSSION

The case material presented indicates some of the diagnostic problems encountered in children with musculoskeletal symptoms where poliomyelitis might be entertained as a possible diag-

nosis. Trauma should always be considered despite a negative history. Swinging from a tree limb is a familiar seasonal pastime and may give rise to a transient palsy involving the brachial plexus roots. A traumatic tenosynovitis of the hip, particularly when associated with a coincidental fever due to a respiratory or gastrointestinal infection (as is commonly seen in summer camps), may be very misleading. Pain with splinting of an extremity should not be confused with weakness or muscle spasm. In other instances, fever may be directly associated with the disability as in tuberculosis or synovitis (coxitis) of the hip joint.

There were no neurological findings in any of the above cases except Case 6. While muscle spasm and pain were present, in some instances atrophy and even shortening of the extremity, there was no specific muscle weakness noted (except Case 6). The character of the pain was generally more localized than one would expect in an early case of poliomyelitis. Referred pain and splinting from a hip or spine disability may give rise to confusing symptoms and findings. Muscle spasm is not necessarily confined to poliomyelitis.

SUMMARY

The association of a fever and constitutional manifestations with localized musculoskeletal findings, occurring particularly during the "polio season," should not be sufficient evidence for a presumptive diagnosis of poliomyelitis in children.

VARIABILITY OF THE POTENCY OF PERTUSSIS VACCINE IN RELATION TO THE NUMBER OF BACTERIA

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ACCORDING to the Biologics Control Law of the United States, each lot of pertussis vaccine prepared under license must meet the government standard of potency and be released by the National Institutes of Health (NIH). The first standard of potency for this vaccine became effective Jan. 1, 1949.[1]

In this paper will be presented an analysis of the potency of a large number of lots of pertussis vaccine recently released. The findings show the fallacy of the use of numbers of bacteria to measure the protective dose for human immunization and the reason the method of determining the potency of pertussis vaccine was changed from evaluation of the bacteria to evaluation of the total human immunizing dose without regard to the number of bacteria per dose provided the number does not exceed a maximum limit.[2]

From the beginning of the use of pertussis vaccine, the dosage was measured in numbers of bacteria. The numbers reported to have afforded substantial protection to the child varied widely (see review by Lapin[3]). They ranged from 22,000 million to 140,000 million for plain bacterial suspensions and 20,000 million to 60,000 million for precipitated bacterial suspensions. On the other hand, some vaccines were reported to be of little or no protective value.[4, 5, 6]

Difference in potency of the bacteria in the vaccines was no doubt an important factor in the results obtained and the lack of agreement on the number of bacteria which should be used for effective protection. The extent of the differences that once existed can be appreciated from the unpublished observations made by the author in 1945 and 1946 on vaccines from fourteen manufacturers in the United States. As determined by the intracerebral mouse protective test, the bacteria in vaccines from three manufacturers had no detectable potency, and differences as much as tenfold existed between the potency of bacteria with demonstrable activity in lots of vaccine from the same and different manufacturers. Recent field trials in England have shown a lack of correlation between protection of children and numbers of bacteria per immunization dose. Two vaccines containing only 60,000 million bacteria afforded significantly better protection than one (plain) containing 90,000 million and two (alum-precipitated) containing 100,000 million and 112,000 million, respectively.[7]

General improvement in the potency of pertussis vaccine in the United States followed the distribution of an outline of an intracerebral mouse protective test to the manufacturers in

From the Laboratory of Biologics Control, National Microbiological Institute, National Institutes of Health, Public Health Service, United States Department of Health, Education, and Welfare.

Presented in part before the Sixth International Congress of Microbiology, Rome, Italy, Sept. 9, 1953.

January, 1946.[5*] This test was adopted later as the official test.[1] By the time the minimum requirements became effective three years later, all but one of the manufacturers were producing vaccines of the required potency. Potency was considered satisfactory if in the mouse test the number of bacteria in the median effective dose (ED_{50}) did not exceed the number in the ED_{50} of the reference vaccine, that is, the potency of the bacteria was measured, but unfortunately without regard to the number in the total human dose which ranged from 30,000 million to 100,000 million. Another factor which contributed to variations in potency of the human dose was that, although the bacteria in all vaccines met the required potency, the bacteria in some ranged up to as much as four times more potent than in other vaccines. The actual extent of variation that prevailed recently is shown in this paper.

MATERIALS AND METHODS

Vaccines.—The data on the 878 lots of vaccines containing antigen for immunization against pertussis and released by the National Institutes of Health during the twenty-seven-month period from Jan. 1, 1951, to April 6, 1953, were reviewed. There were 520 lots of final vaccines finished for distribution and 358 lots of concentrated bacterial suspensions, intended for incorporation in final lots. Fourteen of the final lots and 111 of the concentrates were rejected for inclusion in this study; the former had not been tested against the reference vaccine, Lot No. 4, used in common with the other lots, and the latter were not used in final lots released during the twenty-seven-month period. The remaining 247 lots of the concentrates were used in a part of the final lots from seven manufacturers; one to seven were used in a single final lot. The potency of the final lot was calculated from the proportional amount of each concentrate added, or an average value was taken if the proportional amount of each was not given.

The vaccines contained pertussis bacteria alone, or in combination, with diphtheria toxoid or diphtheria and tetanus toxoids and each without or with a precipitating or an adsorbing mineral adjuvant (potassium aluminum sulfate, aluminum hydroxide, or aluminum phosphate). The number of lots of each product are given in Table I.

The U. S. Standard Pertussis Vaccine.—The reference pertussis vaccine, Lot No. 4, which had been used in the protection test of each lot of vaccine under consideration, was recently adopted as the United States standard. According to the best information available, the total dose of a vaccine equivalent in potency to that of 96,000 million bacteria of the standard would be adequate to afford significant protection to a child. To this number of bacteria of the standard was assigned arbitrarily a value of 12 protective units. The number 12 was selected so that no matter whether there were two, three, or four single injection doses in the total dose, the unit value of each could be expressed by a whole number.

*In this test each mouse is given a single injection of vaccine. Two injections were used in the study reported by Kendrick and associates in 1947 (Am. J. Pub. Health 37: 803, 1947); one injection was used in a later report (Am. J. Pub. Health 39:179, 1949).

The principle of the test grew out of the results of preliminary work by Dr. J. F. Norton in which he made use of the previous experience with *E. typhosa* of Norton and Dingle (Am. J. Pub. Health 25:609, 1935). There was interchange of information between Drs. Norton, Kendrick, and Pittman during the development of the NIH test under the direction of the latter.

Potency Evaluation of the Vaccines.—The potency of the total human immunizing dose of each lot was calculated from the manufacturer's information on the number of bacteria recommended per total dose and the relative mouse protective activity of the bacteria in the vaccine and the reference (standard).

The bacterial count per total dose had been estimated by comparing the bacterial suspension not later than four weeks after harvest with the National Institutes of Health opacity standard. It has been suggested that a vaccine labeled as containing a specified number actually may have a smaller number.[9] The standard was originally adjusted to the opacity of aged vaccines on which direct counts of 10,000 million had been made, but the opacity of the bacterial suspensions for vaccines is determined before aging.

The intracerebral mouse protective test as described in *Minimum Requirements: Pertussis Vaccine* dated March 25, 1948[1] was used to determine the number of bacteria required to protect 50 per cent of the mice (ED_{50}) in relation to the number required for the reference vaccine. Thirteen of the manufacturers used the same number of bacteria per dose in the protective test: 1,500-, 300-, and 60 million. The other three used doses of 800-, 200-, and 50 million; 2,000-, 500-, and 125 million; and 3,000-, 600-, and 120 million, respectively. Sixteen mice usually were used per dose. The ED_{50} was calculated by the Wilson-Worcester method.[10, 11a, b] The formula for calculating the number of protective units per total immunizing dose follows:

$$\frac{ED_{50} \text{ of standard}}{ED_{50} \text{ of vaccine}} \times \frac{\text{No. of bacteria per total dose of vaccine}}{\text{No. of bacteria in one unit of standard } (8 \times 10^9)}$$

Lots of vaccines containing 12 units per total dose were considered as having desirable and acceptable potency; however, because of the rather large probability of error of the mouse test, lower and upper limits of 9.6 and 24 units were set for the results obtained on one test.*

RESULTS

The Unit Value of the Vaccines.—The calculated unit value of the total human immunizing dose of the pertussis component in the 506 final lots of vaccines are summarized in Table I. The values that were obtained from tests with one standard deviation limits within 56 and 178 per cent were separated from those obtained from so-called poor tests with wider limits. There was no detectable effect of the toxoids on the potency of the pertussis component. In the upper half of Table I it is shown that the plain vaccines as a whole had higher values than the precipitated ones and also that more lots had values in the acceptable range of 9.6 and 24 units. Of the lots of plain vaccines, 60.4 per cent had values within this range, while, of the precipitated ones, 52.8 per cent of those tested after the addition of the precipitant and 33.3 per cent of those tested before the addition of the precipitant had values within the same range. A difference in values obtained with and without the benefit of a precipitant would be expected; data on the influence of a precipitating reagent on the mouse protective value will be presented later in this paper.

*The limits of 8.0 and 36 units were set in Amendment No. 2 (July 3, 1953) of Minimum Requirements: Pertussis Vaccine, First Revision (Oct. 31, 1952).

TABLE I. CALCULATED PERTUSSIS UNIT VALUE OF FINAL VACCINES

UNITS PER TOTAL DOSE	1 S. D. LIMITS OF TEST	FINAL PREPARATIONS										CONCENTRATES*				
		PLAIN					PRECIPITATED					BEFORE PRECIPITATION				
		P	DP	DTP	TOTAL	%	D	DP	DTP	TOTAL	%	P	DP	DTP	TOTAL	%
<9.6	Within 56 and 178%	10		2	12	8.6	6	9	47	62	39.0	3	11	69	83	65.9
9.6-24		43	7	34	84	60.4	5	5	74	84	52.8	1	2	39	42	33.3
25-36		18	1	12	31	22.3	2	2	7	11	6.9			1	1	0.8
>36		8	1	3	12	8.6			2	2	1.3					
Totals					139					159					126	
<9.6	Outside 56 and 178%	1			1	4.2			5	5	25.0			7	7	18.4
9.6-24		2		6	8	33.3		1	6	7	35.0		3	10	13	34.2
25-36		3		2	5	20.8			3	3	15.0	1	2	9	12	31.6
>36		5		5	10	41.7			5	5	25.0			6	6	15.8
Totals					24					20					38	
Grand totals		90	9	64	163		13	17	149	179		5	18	141	164	

D, T, and P designate antigenic components, diphtheria toxoid, tetanus toxoid, and pertussis bacteria.
*The potency of the final vaccine was calculated from the tests of the concentrates containing no precipitate.

In the lower half of the table, where the standard deviation limits of the tests were outside 56 and 178 per cent, it is shown that a much larger percentage of the lots in each of the three preparation groups had values above 24 units than in the upper half of the table. This suggests that the poor tests submitted tended to give false high unit values. Tests indicating low potency would have been rejected before submission. The eighty-two lots with poor tests are not included in the analyses given in the remaining part of the paper.

omitted because there was only one lot of each of four and the tests of the lots of the fifth were poor. The given value for each product represents the average value of all of the lots of a manufacturer's product. The number of lots per product in Fig. 1 ranged from 2 to 22. The unitage of a product obtained by averaging the individual lot values has a much narrower limit of probable variation than the single lot values. Measurement of the real value of the product is approached. In Fig. 1, it may be seen that products containing the same

TABLE II. THE UNIT VALUE OF THE PLAIN VACCINES ACCORDING TO THE NUMBER OF BACTERIA PER TOTAL DOSE

NO. OF BACTERIA IN TOTAL DOSE × 10^9	NUMBER OF LOTS				PERCENTAGE OF LOTS		
	UNIT VALUE				UNIT VALUE		
	<9.6	9.6-24	>24	TOTAL	<9.6	9.6-24	>24
60	8	23	6	37	21.6	62.2	16.2
75	2	27	7	36	5.6	75.0	19.4
80	2	7	6	15			
82.5		14	6	20	5.7	60.0	34.3
90		12	15	27			
100		1	3	4		41.9	58.1

Evaluation of the Plain Vaccines According to the Number of Bacteria Per Human Dose.—In Table II is given a compilation of the values of all of the lots of the plain vaccine products according to the number of bacteria per total dose. As the number of bacteria increases the number of lots with values below 9.6 decreases and the number with values above 24 increases. The group containing 75,000 million per dose had the highest percentage that fell between 9.6 and 24 units. It is obvious, however, that potency was not necessarily correlated with the number of bacteria present. This is more evident in Fig. 1, which gives the evaluation of the different products according to the producer. There were twenty-nine products, but five were

number of bacteria per total dose varied considerably in potency. Within the respective dosage groups the differences were 2.5, 2.1, 1.6, and 2.3 fold. Viewed as a whole, potency increased with increase in number of bacteria; the greatest over-all difference was 4.5 fold. Two products, however, containing 60,000 million exceeded one containing 90,000 million, and one of the former exceeded seven others that had 75,000 million or more bacteria per dose.

It is worthy to note that the potency of all but two of the plain products might be considered adequate to afford significant protection. On the other hand, the potency of eight products might be considered to be excessively high.

Evaluation of the Precipitated Vaccines According to the Number of Bacteria Per Human Dose.—In Table III, the lots of all of the precipitated vaccine products are grouped according to the number of bacteria per total dose. The values are separated on the basis of whether the test of the lot was done after or before the addition of the precipitant. In contrast to the observation made on the plain products, potency showed practically no tendency to be in direct relation to the number of bacteria per dose. From

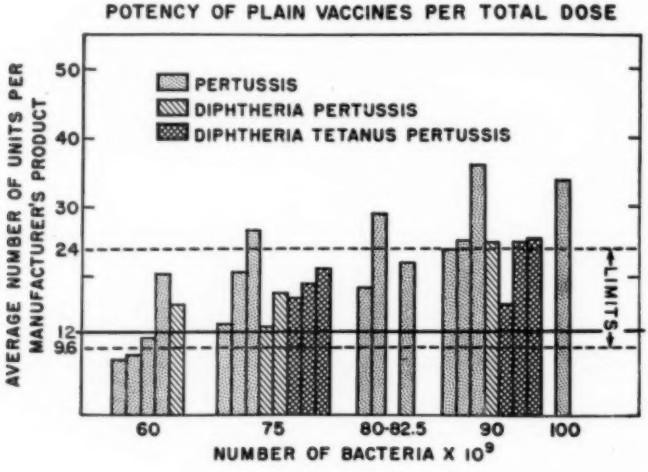

Fig. 1.

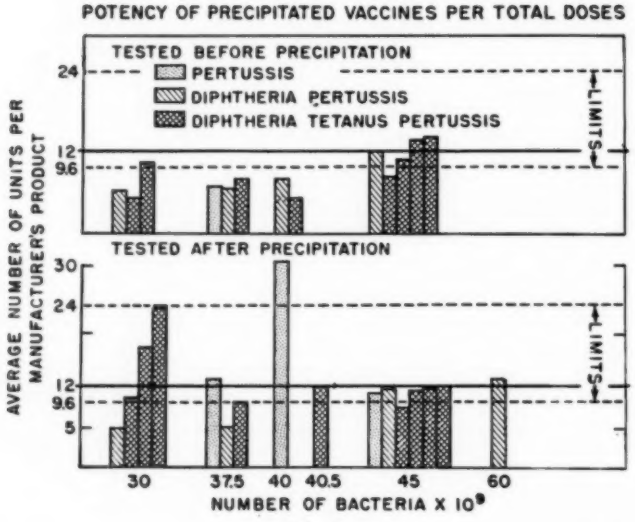

Fig. 2.

the final-vaccine tests, the highest dose group had a larger percentage of lots with values below 9.6 units than the lowest dose group. The largest percentage of lots with values between 9.6 and 24 units was in the 30,000 million dose group. Inconsistencies between potency and numbers of bacteria were also found in the concentrate-tested portion of the precipitated vaccines.

The average potency of lots of each manufacturer's precipitated product is shown in Fig. 2. Eleven single lot products were omitted. As in the table, the values are divided on the basis of tests made on the lots of the products before or after precipitation. Its value of 8.1 units was obtained from the average of tests of seven lots. The potency of only one product exceeded 24 units. The extreme in potency variation was 5.1 fold.

It is difficult to assess the value of the products that were tested before the addition of the precipitant. It is believed, however, that if they had had the benefit of the potentiating action of an adjuvant as will be shown in the next section, the values would have been at least equal to and some better than those of part of the products tested after precipitation. The extreme in potency variation was 3.4 fold.

TABLE III. THE UNIT VALUE OF THE PRECIPITATED VACCINES ACCORDING TO THE NUMBER OF BACTERIA PER TOTAL DOSE

NO. OF BACTERIA IN TOTAL DOSE × 10^9	TESTS MADE ON							
	FINAL VACCINE				CONCENTRATE			
	NO. OF LOTS	PER CENT OF LOTS			NO. OF LOTS	PER CENT OF LOTS		
		<9.6	9.6-24	>24		<9.6	9.6-24	>24
30	59	27.1	62.7	10.2	29	75.9	20.7	3.4
37.5 to 40.5	27	48.1	37.0	14.8	32	90.6	9.4	0.0
45 to 60	73	45.2	50.7	4.1	72	52.7	45.8	1.4

The former products came from eight manufacturers and the latter from seven other manufacturers. Again it is shown that potency was not in direct relation to the number of bacteria present. A difference of fourfold was found in the 30,000 million dosage group of the products tested after precipitation. Two products in this group were more potent than eleven others that contained more bacteria; only one product, containing 40,000 million, exceeded them. It should be mentioned parenthetically that in the protective tests of lots of these two products, lower doses were used than in the tests of the other products. One of the three products that had values below 9.6 contained 45,000 million bacteria.

The Influence of Precipitants on the Protective Activity of Pertussis Vaccine for Mice.—There were twenty-two lots of vaccine from six manufacturers that were tested for potency before and after the addition of the precipitant. The tests were performed under widely varying conditions. At no time were the plain concentrate and the precipitated suspension of a lot tested simultaneously. In some instances, the concentrate was tested by the manufacturer and the final vaccine by the National Institutes of Health. In other instances, the manufacturer tested the final vaccine for purpose of redating, in which case more than one year had elapsed between the two tests. In spite of these variables, there was a signifi-

cant increase in the protective activity after the addition of the precipitant. The calculated unit values of each lot based on the test before and after precipitation are given in Table IV. The average increase for the twenty-two lots was 7.3 ± 1.75 units, or 68.5 per cent.

Comparative tests carried out under more favorable circumstances must be undertaken before a definite amount of potentiation can be ascribed to a mineral adjuvant. Nevertheless, there is no assurance that any value obtained will necessarily hold true for human beings. Correlation of mouse-measured potentiation with potentiation for the child must await properly designed epidemiological studies with vaccines of accurately evaluated mouse protective activities.

It should be mentioned here that the slope of the curve of the mouse response to a precipitated vaccine is sometimes flatter than to the plain vaccines, and greater variability occurs. Slower adsorption of the antigen and slower elimination of toxic substances have been considered as possible interfering factors.

It is of interest to note the difference in the range of potency of the different lots given in Table IV. Before precipitation the range was from 2.7 to 19.7 units, a sevenfold difference, and after precipitation from 3.8 to 32.7 units, an eightfold difference.

The Influence of Repeated Tests on the Acceptance and Rejection of Vaccines.—Since the mouse test has a rather large probability of error, a question naturally arises in regard to the acceptance of vaccines that are too low or too high in potency and the rejection of good vaccines, when total dose values that fall between 9.6 and 24 units are accepted for the designation of 12 units. The influence of replica tests on the acceptance and rejection of vaccines is therefore of special interest. Data on some lots of vaccines under consideration in this paper are given in Tables V and VI. In Table V is given the evaluation of 124 lots on the basis of duplicate tests. Each lot met the minimum requirements for potency then in effect. The values in Table V, however, are given as acceptable if they fell between 9.6 and 24 units and rejective if outside these limits. The acceptable or rejectable status of seventy-one of the 124 lots (57.3 per cent) were the same on each test; thirty-three lots that had re-

TABLE IV. THE INFLUENCE OF A PRECIPITANT ON THE MOUSE PROTECTIVE ACTIVITY OF PERTUSSIS VACCINES

SERIAL LOT NO.	UNITS			SERIAL LOT NO.	UNITS			SERIAL LOT NO.	UNITS		
	BEFORE*	AFTER*	DIFF.		BEFORE	AFTER	DIFF.		BEFORE	AFTER	DIFF.
1	6.5	9.6	3.1	9	6.5	20.4	13.9	17	5.0	23.7	18.7
2	8.2	12.8	4.6	10	7.4	28.6	21.2	18	6.4	7.8	1.4
3	12.9	11.6	−1.3	11	3.5‡	3.8	0.3	19	6.7	18.0‡	11.3
4	19.0	9.0	−10.0	12	3.8	8.1	4.3	20	9.3	19.4	10.1
5	2.7	5.9	3.2	13	31.9†	45.5†	13.6	21	42.5†	60.7†	18.2
6	5.5	12.2	6.7	14	4.4	10.3	5.9	22	19.7	23.7	4.0
7	11.8	32.7	20.9	15	9.5	3.9	−5.6	Av.	10.8	18.2	7.3 ± 1.75
8	8.2	17.4	9.2	16	7.3	14.3	7.0				

*Before and after the addition of the precipitant.
†One standard deviation limits exceeded 56 and 178 per cent.
‡Average of two tests.

jectable values on one test had acceptable average values, and twenty lots (16.1 per cent) that had acceptable values on one test had rejectable average values.

There were very little data available where there had been three or more tests on a lot. One manufacturer prepared large lots of concentrates, and the same concentrate was used in several final lots. The tests on final lots trate, would be an acceptable value. Two tests of Lot D, with a rejectable average, gave acceptable values; only if these two of the four values were averaged would an acceptable average be obtained. All test values of Lot E were rejectable.

From the data presented, it is shown that the use of duplicate tests decreases the chances of accepting poor

TABLE V. THE INFLUENCE OF TWO TESTS ON THE ACCEPTANCE AND REJECTION OF VACCINES

TEST MADE BY	NO. OF LOTS	1ST TEST			2ND TEST			AVERAGES			EFFECT OF AVERAGE			
		A	R		A	R		A	R		NO CHANGE		INCREASE	
		9.6-24	<9.6	>24	9.6-24	<9.6	>24	9.6-24	<9.6	>24	A	R	A	R
Manufacturers	44	18	17	9	29	9	6	29	9	6	13	8	16	7
NIH	10	3	7		2	7	1	2	7	1	1	6	1	2
Manufacturers NIH	70	22	35	13	29	32	9	29	32	9	13	30	16	11
Totals	124	43	59	22	60	48	16	60	48	16	27	44	33	20

A = Acceptable.
R = Rejectable.

Proportion of lots not affected by average value	71/124 = 57.3 per cent.
Proportion of lots increased in acceptance	33/124 = 26.6 per cent.
Proportion of lots increased in rejection	20/124 = 16.1 per cent.

TABLE VI. MULTIPLE TEST EVALUATION OF VACCINES

NUMBER OF FINAL LOTS	UNIT VALUE OF LOTS CONTAINING SAME CONCENTRATE				
	CONCENTRATE LOT				
	A	B	C	D	E
1	8.0	6.8	5.7	5.1	3.8
2	15.7	18.1	13.6	8.3	6.8
3	16.8	19.7	19.0	10.2	7.3
4	19.4			10.3	8.1
Average	15.0	14.9	12.8	8.5	6.5

containing a common concentrate could be considered as multiple tests on a single lot of concentrate. Values of final vaccines in which five concentrates were used are given in Table VI. The average values of three concentrates were acceptable and of two rejectable. One test of each of the former has a rejectable value; but this value, if averaged with any one of the other values for the respective concen-

vaccines and of rejecting good vaccines. In the five examples given, the use of three or four tests did not alter the status of the vaccine that would have been obtained with the average of any two tests, except in one instance. The chances of accepting vaccines of potency just below the lower limit are decreased with the use of more than two tests. Since multiple tests increase the precision of meas-

urement, it might be advisable not to accept a vaccine with an average value on the lower limit of 9.6 units per total dose.

DISCUSSION

The analysis given in this paper shows that, since the introduction of a laboratory test for potency in 1946, there has been much improvement in the mouse protective activity of pertussis vaccine; nevertheless, wide differences in the potency of the total dose intended for human immunization and measured in numbers of bacteria were still prevalent up to the early part of 1953. These differences were not attributable solely to the number of bacteria per dose. The existing differences prompted a change in potency requirements based on the value of the total human dose instead of the bacteria incorporated in the vaccine. The revision printed on Oct. 31, 1952,[2] to be effective May 1, 1953, went into effect Aug. 1, 1953. Because of the probable error of the test, some differences will continue to exist but within narrower limits. Originally the limits of 9.6 and 24 units were set for the value obtained in one test for a vaccine that could be accepted as having 12 units per total dose. An amendment changed the limits to 8.0 and 36 units. This was done because of the greater variations that occurred in potency tests of precipitated vaccines. From the data given here, it is evident that the majority of the lots of vaccines released under the old requirement had values within the narrower limits. It is therefore reasonable to suggest that as testing is improved fewer and fewer lots of vaccines will have values outside the narrower range.

The potencies of the products which present a more precise evaluation of the human immunizing dose than the values of individual lots shows the marked differences that were existing between the products having either the same or different numbers of bacteria. Differences which ranged up to fourfold in products having the same number of bacteria suggest that there is need for more information on how to produce a vaccine with maximum potency per bacterial cell.

It seems definite that the larger numbers of bacteria formerly recommended for human immunization are no longer indicated. With the plain products there were eight of twenty-four that had values greater than 24 units. These as well as others should have provided at least 12 units in doses of 60,000 million bacteria or less. On the other hand, three of five products containing 60,000 million had less than 12 units per dose, two containing 75,000 million had no more than 13 units, and even one containing 90,000 million had no more than 16 units.

The vaccines containing a mineral adjuvant were more difficult to evaluate than the plain ones; some were tested before the addition of the adjuvant. It was found that for the mouse the adjuvants increased the protective activity by about 70 per cent. The comparative tests were not performed under the most desirable circumstances. In some instances there was no potentiation; this may or may not have been due to variability of the test. Testing of a precipitated vaccine is complicated by the fact that a plain vaccine is used for reference and the slope of the response curves

are not always parallel. Nevertheless, the use of a precipitated reference vaccine has not seemed practical. Three adjuvants, each in varying amounts, are in use. As a whole, the precipitated vaccines were lower in unitage than the plain products. There is no available information on the relative protentiation of the adjuvants in mice and in children. Re-evaluation of the benefits that children derive from the use of mineral adjuvants with pertussis vaccine is needed. It has been shown that pertussis vaccine increases the efficacy of diphtheria toxoid in guinea pigs[12] and that the potentiation is as great as when aluminum phosphate is used.[13] Substantial protection against pertus- adjuvants.[7, 14] Sako and associates[15] showed that very young infants could be effectively immunized with an alum-precipitated vaccine. It is not known what would be the difference in response to vaccines with and without an adjuvant but of the same potency.

Besides reducing the wide differences in the potency of the human dose, the limitation in the unitage of a vaccine should tend to reduce the untoward reactions that sometimes follow both primary and booster injections. There are some indications that potency and reactive factors in pertussis vaccine may be correlated but not necessarily interrelated. A concomitant loss in dermonecrotic toxicity and mouse protective activity has been reported.[9] Reactions in children, however, are probably not caused by this toxic factor, as the vaccines when released do not cause dermonecrosis in rabbits. This toxin might play a role if improperly aged suspensions or living bacterial vaccines recently reported to be under investigation[16] were used. The incidence of reactions from booster doses has been greater than that from primary immunization injections. The use of vaccines with measured potency should be helpful in determining the amount of vaccine that is needed for booster immunization. It has been customary to use one single injection dose. As now distributed, single doses of different products contain 3, 4, or 6 units, respectively. Volk, Top, and Bunney[17] obtained serological stimulus and a decrease in reactions with the use of one-half of a single injection dose. The question arises: what was the unitage of the vaccine used?

Finally, the use of units to express the potency of a vaccine will facilitate the evaluation of bacterial fraction vaccines. Two methods of partial purification have been published.[18-20]

As newer knowledge becomes available it is hoped that further steps may be taken toward the goal of adequate protection without untoward reactions.

SUMMARY AND CONCLUSIONS

An evaluation of many lots of pertussis vaccine recently released by the National Institutes of Health has shown wide differences in the laboratory-evaluated potency of the total human immunizing dose. The number of bacteria per total dose ranged from 60,000- to 100,000 million for the plain saline suspensions and 30,000- to 60,000 million for the precipitated suspensions, but potency was not necessarily correlated with the number of bacteria present. Products containing the same number of bacteria showed differences as great as fourfold, and some products were more

potent than others containing more bacteria; between all final products the extreme in difference was 6.2 fold.

Only two of twenty-four plain products were lower in potency than the lower limit set for the defined immunizing dose of the United States standard, but eight were greater in potency than the upper limit. Three of sixteen finished precipitated products were below and one above.

A comparison of the potency of a large number of bacterial suspensions before and after the addition of a mineral adjuvant showed an average increase of 68.5 per cent in mouse protective activity.

The use of at least two tests to evaluate the potency of a lot of vaccine would reduce the chances of accepting poor vaccines and rejecting good vaccines. Replicas increased the precision of potency evaluation.

The clinical use of a defined number of units as determined by the mouse protective test should reduce the wide differences in immunity that have been reported following vaccination with doses measured in numbers of bacteria. On the one hand, the probability of the use of vaccines that are inadequate to induce immunity should be reduced; on the other hand, it should be possible to avoid the use of excessive dosage and thereby probably reduce the incidence of reactions.

Grateful acknowledgment is extended to Mr. James F. Marshall and Mr. George E. Grubbs for the calculations of the ED_{50} and the unit value of each lot of vaccine and for the performance of the mouse protection tests at the National Institutes of Health.

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DIETARY SUPPLEMENTATION OF VITAMIN B_{12} IN PREPUBERTY SCHOOL-AGE CHILDREN

I. Growth Studies

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THIS study was undertaken to determine the effect of vitamin B_{12} on growth, nutritional signs and deficiencies, and on deafness and blindness. Our decision to conduct the study was on the basis of published reports of the effect of vitamin B_{12} in child growth,[1, 2] and preliminary unpublished data which suggested that treatment with this vitamin might be beneficial in deafness and possibly in optic nerve lesions. Our observations on the effect of daily oral administration of vitamin B_{12} on the growth of prepuberty school-age children will be the subject of this paper. Further analysis and evaluation are required before the other phases of our study can be reported.

The Ohio State School for the Deaf and the Ohio State School for the Blind were chosen for our study, since these two institutions fulfilled the various requisite conditions. Approximately 500 children of school age (6 to 17 years) were enrolled. They were healthy and normal in every respect except for the sight or hearing disorders involved. Regarding physical activity of the groups, the children from the School for the Deaf were in no way different from ordinary school children. At the School for the Blind, however, physical activity was understandably restricted, but the children all participated in active sports and thus cannot be considered sedentary.

In these boarding-type schools the children's meals were planned and supervised by trained nutritionists and dietitians and conformed nutritionally to the National Research Council's standards. Little, if any, opportunity was offered for excesses or significant alterations in the dietary intake. In addition to the controlled diet, each child in the entire study group received a daily multiple vitamin supplement containing 1 μg of vitamin B_{12} activity.

The study was designed so as to take the fullest possible advantage of randomization; the control and test groups were selected by roster, alternate names being placed in the control group or the test group, respectively. By means of this plan, children from a single class were in both groups, and they all attended class together, ate together, and slept in

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the same dormitories. In this way complete randomization was achieved.

The test medications were given at the noon meal which was the main meal of the day. Vitamin B_{12}* was administered as 20 μg tablets. Placebo tablets were used for the control group, and corresponded exactly in shape, color, and taste to the vitamin B_{12} tablets. The two types of tablets were designated X and Y, and the teachers and school nurses administered them to the students by roster. Neither the school personnel nor the professional staff of physicians and nurses who observed the children in the study knew which type of tablet contained the vitamin B_{12}, and this was not revealed until the study was completed, the data analyzed, and the conclusions made.

Most of the children in the Schools for the Deaf and the Blind had been at home for the summer vacation. All returned to school in early September. A preliminary four-week control period was allowed in order to eliminate, as nearly as possible, any undesirable dietary or nutritional influences remaining from the vacation period.

At the start of the study each child was given a complete medical examination, including a detailed nutritional physical evaluation. Blood counts and hemoglobin determinations were made, and color photographs were taken of characteristic nutritional lesions observed. None of the children in either school had acute or chronic disorders which could be considered to have any potential influences on growth. Height and weight records were available from previous years, and measurements were made at the beginning of the study. Additional height and weight measurements were recorded at mid-term and again at the end of the school year, the following May. At that time, physical and nutritional examinations also were made and follow-up photographs were taken. In the School for the Deaf, serial audiograms were taken at intervals during the study on those children who had records of prior tests.

In our study on growth, only the data on the prepuberty children were analyzed. The age of 10 was arbitrarily chosen as the dividing line between the puberty and the prepuberty age groups. Our criterion may have been unnecessarily rigid since by such differentiation a large number of children were automatically eliminated from this phase of the study; in addition, all children who were 10 years old by the time the study was completed were not included. Furthermore, any child who contracted a serious illness of a duration longer than two weeks was excluded, since our study was to deal with the effect of vitamin B_{12} upon normal, healthy children. Fortunately, no epidemics occurred during the test period which might have seriously influenced the results. A number of children were lost from the study group by virtue of transfers or removal from school.

Of more than 500 children originally examined, 132 remained that could justifiably be classified as normal and of prepuberty age. Of these, as was determined after completion of the study, sixty were found to have been in the test group and seventy-two in the control group.

*The vitamin B_{12} used in the study was supplied by Merck & Co., Inc., Rahway, N. J.

The X tablet used in the study was revealed to have contained the vitamin B_{12}.

Because of the wide range of variables which could be anticipated in a study of this kind, it was necessary to use special methods of statistical analysis: (1) variance analysis, and (2) regression analysis. By these intricate procedures, relationships between weight, height, and nutritional status could be evaluated and interpreted.

The average weight gain over the eight-month period for the children in the vitamin B_{12}-treated group was 4.50 pounds ± .53 pound. The control group gain averaged 3.80 pounds ± .48 pounds. The difference was 0.71 ± .072 pound in favor of the vitamin B_{12}-treated group. Because of wide variation in weight gains, this figure was not significant by "standard methods" of statistical analysis.

It must be pointed out that the accepted or "standard method" of statistical analysis of studies of this nature does not take into account the growth status of individual children; rather it tests the difference in the average of groups.

One should not expect a vitamin to produce an effect upon normal children. If it did, it could no longer be considered a vitamin but a pharmacologic agent instead. Furthermore, underweight children should not justifiably be compared in a growth study with overweight children; in turn, it is unreasonable to apply "standard method" statistical analysis in a comparison of overweight children and normal children when the effects of a growth-promoting factor are being evaluated. These details had been considered when the study was designed and, before the sealed envelope which contained the identity of the X and Y tablets was opened, the data were analyzed from the standpoint of the type of individuals affected, if any, i.e., underweight, normal, or obese children.

RESULTS

The results indicated that an unexpected relationship existed between the X (vitamin B_{12}) and Y (placebo) groups. We found that statistically significant weight increases had occurred in the underweight or thin children treated with vitamin B_{12} as compared with the underweight or thin children to whom the placebo tablets had been administered. The normal children from both vitamin B_{12} and control groups showed no difference. In contrast, data on the overweight children in both groups showed a very slight weight gain in the vitamin B_{12} group. While this was statistically significant, it was not in the high range of significance. However, it was apparent that the influence of vitamin B_{12} on the underweight children was great enough to carry the total group (underweight, normal, and obese) almost to statistical significance.

The data were further examined to determine whether any effect on height had been obtained. As before, when the effects on the total group were measured, no statistically tenable differences were observed. However, we were surprised to find that in the underweight children no appreciable improvement in the rate of height gain was obtained. This applied also for the normal children. Examination of the overweight children revealed that statistically sig-

nificant increases in the rate of height gain had occurred in the vitamin B_{12}-treated group as compared with the height gain in the placebo-treated overweight group.

While these effects on height gain were unforeseen, there is no doubt but that the changes did take place. Our observations will have to be confirmed in other studies, however, before final conclusions can be made.

In regard to other phases of our study, the data on the nutritional signs and findings have not yet been analyzed, nor have those on the audiogram readings. It is apparent, however, that no outstanding beneficial effect was produced in the cases of nerve deafness or in the various types of optic nerve involvement. It was our impression that a number of nutritional signs had changed in some of the children; this evaluation will be the subject of a later report.

CONCLUSIONS

We feel that this study confirms the reports of Wetzel,[1] Chow,[2] Jolliffe,[3] O'Neil,[4] Doraiswamy,[5] Sunder Rao,[6] Wilde,[7] and their co-workers in that vitamin B_{12} provides a beneficial effect upon weight gain in underweight children. The degree of effect apparently is related directly to the degree of underweight. We also believe that the evidence of the slight but statistically important increase in height gain in overweight children may suggest that vitamin B_{12} plays a role in some fundamental metabolic growth-regulating mechanism. In addition we feel that this study has conclusively demonstrated that no supernormal effect is produced by the administration of vitamin B_{12} since there was no effect whatsoever on height gain or weight gain of normal children.

Because of these unexpected findings, we obtained a consultation with Dr. John W. Tukey* for further interpretation. He suggested that from the physician's standpoint in treating the underweight children it may be more desirable to have a greater degree of increase in weight than in height. Conversely, in the growing child who is overweight, it would be therapeutically more desirable to obtain a greater increase in the rate of height gain than in weight gain.

Various growth charts† were considered in the process of selecting one to serve as a guide in classifying the children in their appropriate underweight, normal weight, and overweight groups. The Wetzel Grid channel system seemed to answer our purposes satisfactorily. By this system, the children who fell in the normal or B-1 channel were considered of normal weight, while those who fell in B-2, 3, or 4 or beyond were considered underweight; for the overweight children, those in channel A-1 were considered of normal weight and those beyond were considered overweight. Clinical sampling confirmed the distribution.

SUMMARY

As final members of the group in a controlled study during a school year, 132 school-age, prepuberty children were divided at random into two groups. One group received vitamin B_{12}, the other group, a placebo. Our results confirm earlier reports that

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†Wetzel Grid. Nelson, W. E.: Mitchell-Nelson Textbook of Pediatrics, ed. 5, Philadelphia, 1950, W. B. Saunders Co. Metropolitan Life Insurance Growth Rate Charts.

vitamin B_{12} increases weight gain in underweight children. It has no effect on height or weight gain in normal children, and it appears to increase the rate of height gain in overweight children.

Acknowledgment is made of the cooperation and suggestions of E. R. Abernathy, Ph.D., Superintendent, Ohio School for the Deaf, and W. G. Scarberry, M.A., Superintendent, Ohio School for the Blind.

We also express our appreciation to the nurses of the respective schools, Miss Beatrice South, R.N., and Mrs. Lena Gram, R.N., without whose assistance the study could not have been conducted.

We are indebted to Fred W. Cleveland, Jr., of the Industrial Engineering Department of Merck & Co., Inc., for the statistical analysis of these data.

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DUODENAL ULCER IN CHILDREN WITH HEMORRHAGE AS THE PRESENTING SYMPTOM

Report of Three Cases

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RECENTLY we have had the unusual opportunity of seeing three cases of duodenal ulcer in children, the presenting symptom of each being present or recent gastrointestinal hemorrhage.

In recent years, the reported frequency of peptic ulcers in infants and children has had an apparent increase due undoubtedly to the greater awareness of physicians of this possibility. Ever since Bird and associates[1] reported the first large series of 243 cases of peptic ulceration in children, diagnosed both by operation and at autopsy, further studies have reported many additional cases. In 1952, Jenkins[2] published a report in which he summarized the findings in eighty cases in which definite x-ray evidence of peptic ulceration was present. These cases were observed over a twelve-year period and occurred in children between 4 and 14 years of age. An interesting finding was the predilection for boys in a ratio of 8:1. This observation differs from that of Girdany,[3] whose findings are that both sexes are equally affected. Our three patients were boys.

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Previous reports have stressed the importance of the history in children with this condition. Especially with a history of recurrent abdominal pain should one's suspicions be aroused. If this pain is particularly severe at night and is present on arising in the morning it is even more suggestive. The pain may often be well localized to the upper midepigastrium, and tenderness may be elicited on physical examination.

While hemorrhage can certainly be a complicating feature of peptic ulcers in children as well as in adults, we were unable to find specific mention of it as a prominent or frequent presenting symptom. In the past when a pediatrician or surgeon has been faced with the problem of undetermined gastrointestinal hemorrhage in a child, the first thought was usually of a Meckel's diverticulum or multiple intestinal polyps rather than peptic ulcer. McAleese and Sieber[5] mention the infrequency of peptic ulcer as a cause of gastrointestinal hemorrhage in children.

The three patients whom we observed were admitted to University Hospital because of gastrointestinal hemorrhage, and their course is summarized.

CASE REPORTS

CASE 1.—T. O., a 10-year-old boy, was admitted to University Hospital on Oct. 27, 1953, with a three-day history of weakness and headache and a story of having a dark tarry stool two days prior to admission. In addition to this, he appeared pale and sallow to his parents. There was no history of nausea, vomiting, or persistent abdominal pain in the past. The appetite had always been good, and there was no suggestion of gastrointestinal disease prior to the present illness.

At the time of admission the boy appeared pale and lethargic but in no acute distress. The pulse was 90, blood pressure was 92/58, and respirations were 24. On abdominal examination there were no organs or masses palpable, and no tenderness was elicited. Rectal examination was negative except for the presence of tarry stool on the examining finger.

Laboratory studies included a hemoglobin of 8.4 Gm., red blood count of 2.32 million, white count of 6,200 with a normal differential, bleeding tinme of 4 minutes and clotting time of 11 minutes. Platelets were adequate on examining the smear. Stool was 4 plus on guaiac examination.

On the day following admission the hemoglobin had fallen to 7 Gm., and the boy was transfused with 500 c.c. of whole blood. At this time an upper and lower gastrointestinal examination was performed. The upper gastrointestinal series revealed a persistent filling defect along the distal upper border of the duodenal bulb under fluoroscopy. The films confirmed this finding, showing the ulcer crater on the anterior wall of the duodenal bulb. There was no other abnormality of the gastrointestinal tract noted.

Once the diagnosis of peptic ulcer was established, treatment was instituted and consisted of bland feedings with interval feedings of milk and cream, belladonna and phenobarbital mixture, Amphojel and ferrous sulfate. No further transfusions were necessary. By the seventeenth day in the hospital the hemoglobin was 11 Gm., red blood count was 4.5 million, and stools were persistently free of blood. An upper gastrointestinal series repeated ten days after the first examination did not show any change from the previous one. However, films taken subsequent to discharge on Jan. 4, 1954, did show almost complete healing of the duodenal ulcer.

CASE 2.—D. B., a 13-year-old boy, was admitted to University Hospital on Nov. 6, 1953, with a three- to four-week history of abdominal pain. This pain was not well localized and was relieved almost entirely by eating. The pain might last for several days and then disappear, to recur a few days later. Three days before admission the patient vomited bright red blood on one occasion, and following this tarry stools were noted. He was observed by his family physician for forty-eight hours, then was referred to this hospital when it appeared that the bleeding was not going to stop after the boy had been kept in bed and fed only milk.

On admission, the boy appeared pale, restless, and weak. The pulse was 100 and the blood pressure 120/66. The skin appeared moist and pale. There were no organs or masses palpable. On rectal examination there were no abnormalities of anus or sphincter, but there was some tarry stool noted.

Laboratory studies included a hemoglobin of 7 Gm. and a white blood count of 14,700, with a shift to the left. Platelets appeared adequate on the smear. Bleeding time was 6 minutes and clotting time 12 minutes. Rumpel-Leeds test was negative.

An emergency upper gastrointestinal examination with fluoroscopy was taken after the boy had first received 1,000 c.c. of blood during the first forty-eight hours in the hospital, and this did not show any evidence

of pathology which could explain the present bleeding. The duodenal bulb was fairly well visualized, and no ulcer crater was seen. However, the boy continued to bleed, passing fresh blood and tarry stool per rectum. He received an additional 1,000 c.c. of blood during the next forty-eight hours in divided transfusions and was only taking milk by mouth. While this boy was being prepared for a barium enema, he passed considerable amounts of fresh blood and appeared acutely ill following this episode. He received an additional transfusion and was considered to have reached the stage where an emergency exploratory laparotomy was indicated.

On the evening of the fourth hospital day a laparotomy was performed, at which time a bleeding duodenal ulcer was discovered and was given surgical treatment. The stomach was opened, and on the anterior superior wall of the duodenum just distal to the pylorus an ulcer was noted approximately 8 mm. in diameter, which was oozing bright red blood. Catgut sutures were laced across the ulcer in order to attempt to obliterate it. In addition, two vessels on the serosal surface that were feeding the area of the ulcer were ligated. The rest of the gastrointestinal tract was examined, and no other pathology was noted.

Postoperatively there were no complications. Wangensteen suction was used at first, and additional fluids and blood were administered intravenously. A typical adult ulcer regimen was followed later with a Meulengracht diet, interval feedings of milk and cream, belladonna, alkali therapy, and ferrous gluconate. The patient was discharged on the twenty-third hospital day.

CASE 3.—J. L., a 7-year-old boy, was admitted to University Hospital on Nov. 4, 1953, with a five-month history of abdominal pain and fatigue. Six months prior to admission he was found to be severely anemic with a hemoglobin of 35 per cent and a red blood count of 1.6 million and received two blood transfusions in another hospital. Four months later he had another episode of abdominal pain followed by vomiting of dark brown gastric contents and later blood clots. An enema at home produced a tarry stool. He was again hospitalized elsewhere and transfused when the hemoglobin was 30 per cent and the red blood count 1.2 million. He was admitted to the University Hospital two months later for evaluation of recurrent gastrointestinal bleeding.

The past history revealed that he always bruised easily, but that there was never any specific note made of hemarthroses, hematuria, or severe epistaxis. At birth a diagnosis of erythroblastosis fetails was made because of anemia, mild icterus, and confirmatory blood studies. At the time of discharge from the hospital at 2 weeks of age the boy was considered to be severely brain damaged because of a poor suck, extreme lethargy, and a weak Moro reflex. However, his general motor development subsequent to these original impressions had been quite normal. Family history was of importance in that we could elicit no evidence of blood dyscrasia.

At the time of admission the patient appeared to be a well-developed boy of stated age in no acute distress. There were no areas of ecchymosis, purpura, or petechiae noted over the skin. General physical and neurological examination was not remarkable. There were no abdominal organs or masses palpable, nor was there any tenderness. A left external divergent strabismus was noted.

Laboratory studies included a hemoglobin of 12.2 Gm., red blood count of 3.69 million, and a white count of 6,800 with a normal differential. Platelet count was 162,000. Bleeding time was 2 minutes 30 seconds (normal time, 2 to 4 minutes, method of Duke) and four clotting

times were variously reported as 19 minutes, 15 minutes 30 seconds, 24 minutes 30 seconds, and 16 minutes 40 seconds. The three-tube Lee-White method was employed and any reading up to 15 minutes is considered normal.

Shortly after admission an upper gastrointestinal series with fluoroscopy was carried out, and this showed a persistent deformity of the duodenal bulb. This was noted both at fluoroscopy and on the films. The impression was that this represented a healing phase of a duodenal ulcer that had been recently active. Ten days later a repeat x-ray examination was performed and this time was reported as showing the same deformity and fleck in the duodenum that had been previously present. The deformity seemed to be less pronounced and the fleck somewhat smaller than on the previous examination.

Although the duodenal ulcer present in this patient appeared to be healing satisfactorily, it was considered wise to institute a dietary program. Accordingly, before the boy left the hospital dietary recommendations were made that included the use of bland feedings with the avoidance of heavily seasoned and salted foods and the use of interval milk feedings between meals.

Comment on Case 3.—The fact that four separate clotting time determinations were abnormally prolonged made us consider an additional diagnosis of hemophilia, but no definitive blood studies were undertaken at this time that might have proved this diagnosis. However, the prolongation of the clotting time might certainly be considered a factor in the recurrent bleeding of the peptic ulcer described by roentgenogram.

DISCUSSION

These three children, in whom peptic ulcer was eventually diagnosed by means of roentgen study in two and by an exploratory laparotomy in one, are similar in that the major complaints prior to admission were related to the presence of bleeding manifested either by vomiting of blood or by loss in the stool. While there was a previous complaint of abdominal pain in two of these three boys, it was not the striking feature of the history. The symptoms of peptic ulcer in children of the older age group are very similar to those of adults with this condition. First symptoms, therefore, can either be the traditional recurrent, upper abdominal pain or hemorrhage as pointed out by these three cases.

In reviewing the recent literature, we were unable to find any large series of children with this condition who have been studied carefully from a psychiatric viewpoint with an attempt made to evaluate their emotional make-up. Girdany[3, 4] describes the older children in his series as being quite similar to their adult counterparts in their reactions. They are usually considered bright, nervous, and tense and often seem lacking in emotional liability.

The psychiatric consultant who saw these three children and their parents found certain features common to these patients. In all of them there were multiple inner tensions present, and the children tended to keep things to themselves. One of them was quoted as saying, "I think that one of my troubles is that I have to say yes—even when I feel like saying no."

An attempt was made to evaluate the home situation and the families of these children in an attempt to unearth some of the tensions that might be present. None of these children were considered amenable to

long-term psychotherapy. However, the mother of one of our patients was found to be sufficiently disturbed so that a program of psychiatric assistance was offered.

SUMMARY

1. Three cases of peptic ulcer in older children are presented.

2. The clinical course indicates that gastrointestinal bleeding may be the first sign of the presence of an ulcer and an early complication of this condition.

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MYASTHENIA GRAVIS WITH MENTAL RETARDATION

Report of a Case in a 10-Year-Old Boy With Special Reference to Electromyographic Studies, Psychological Evaluations, and Autopsy Findings

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MYASTHENIA gravis in children is of such rare occurrence that many pediatricians may pass a lifetime without encountering a single case.

Levethan and associates,[1] in 1941, reported only thirty-four cases in patients under 17 years of age and eight under 10 years of age. Nilsby,[2] in 1949, found thirty-five cases under 17 years of age and eight under 8 years of age. Tunestam,[3] in 1950, reported thirty cases among children under 10 years of age.

The explanation for the small number of cases reported is not only the fact that the condition is rare but that the disease is hard to recognize in a child. The *myasthenic crisis* that is well known in adults is seldom recognized in children. Levethan and co-workers,[1] Lieberman,[4] and Bastedo[5] called attention to the myasthenic crisis in children and stressed the importance of immediate treatment. Schwartz[6] described a case of myasthenic crisis in a child of 7 that simulated bulbar polio so closely that it was at first diagnosed as such.

As a result of improved diagnostic facilities, more cases of myasthenia gravis are being recognized of late. Reports have appeared recently of myasthenia gravis in the newborn infant.[7]

We are presenting a case of myasthenia gravis in a young child, which had to be differentiated from bulbar poliomyelitis. The case, we feel, is of added interest because the child was also mentally retarded.

Myasthenia gravis with psychiatric symptoms has been described in medical literature[8, 9, 10] but a combination of myasthenia gravis and mental retardation has not, to our knowledge, been reported previously. Our studies include the effect of Prostigmine on the mental reaction of the child, and electromyography, psychological evaluations, and post-mortem findings.

CASE REPORT

T. H., a Negro male 10 years of age, was admitted to the Cook County Children's Hospital, Sept. 8, 1951. His mother stated that a few hours before being brought to the hospital the child had difficulty in breathing and swallowing and coughed a great deal. For the past six months, the mother reported, the child fumbled and found running and stair climbing very difficult. He had to use both hands to lift a glass to his mouth.

The child was born prematurely (spontaneous delivery); birth weight 4½ pounds. There were no cyanosis, jaundice, or convulsions during the neonatal period; no Rh factor. The

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mother was gravida i, para i. Mother was 31, father 32, at birth of child. There was no history of muscular weakness in the family; no consanguinity.

The patient was breast fed up to 4 months. He had orange juice and cod-liver oil daily. The child sat up at 6 months, walked at 12 months, talked at 2 years. He had triple toxoid and smallpox vaccinations.

On admission the temperature was 102.4° F. The patient complained of pain in head and neck. He was able to bend the back and neck but action was painful. There was a head drop and ptosis of the left upper eyelid with left divergent strabismus; pupils reacted to light; lids did not close well. There were some secretions in the pharynx and poor gag reflex. Kernig's sign was negative. The chest was loaded with rhonchi but no actual râles The heart was normal and the liver and spleen not palpable. Reflexes were hypoactive. He moved the extremities with great difficulty.

A provisional diagnosis of bulbar poliomyelitis was made. However, because of the patient's poor condition, a lumbar puncture was considered inadvisable. Emergency tracheotomy was done. The patient was placed in a postural drainage position and the secretions aspirated. Penicillin was given parenterally. Three hours later the child showed some improvement. The temperature dropped to 99° F. There were no symptoms of acute distress. The patient was able to walk, and to breathe through the mouth. There was no head drop. The pupils reacted to light and accommodation with occasional nystagmus. There was no difficulty in swallowing and no pooling of secretions. Gag reflex was intact. Heart and lungs were normal, abdomen negative. Extremities were slightly hypotonic, and deep tendon reflexes diminished.

The following morning the child again had difficulty in breathing and in swallowing. He had drooling saliva from mouth, ptosis, a nasal twang and head drop but no neck rigidity on flexion. There were no extraocular muscle paralysis and no asymmetry of the face. The tongue could be moved in all directions. The temperature rose to 100° F. Pharyngeal reflex was sluggish with pooling of secretions. The heart was normal; the chest was loaded with rhonchi but no retraction was evident. Abdominal reflex and knee jerk were present. The liver and spleen were not palpable.

The patient was placed in the Trendelenburg position and the secretions aspirated frequently. Complete bed rest was enforced, and 300,000 units penicillin administered. The patient improved gradually. However, on the third day of hospitalization, he still had difficulty in breathing. Fluid still regurgitated through the nose occasionally. Nasal twang was still present.

On the fourth day of hospitalization, a diagnosis of myasthenia gravis was made and 1 c.c. of 1:4,000 Prostigmine was given intramuscularly. Ten minutes later considerable improvement was noted in the muscle tone. Ptosis decreased (Fig. 1). Activity increased. During the next three days, the patient was placed on Prostigmine 1:2,000 intramuscularly every six hours. Improvement was very marked after treatment. His speech became more distinct. Saliva no longer drooled from mouth. The patient swallowed fluids without difficulty. Ptosis disappeared. The child became alert and wanted to get out of bed and play with the other children in the ward. Oral Prostigmine, one tablet four times daily, was prescribed, with good results following. The patient was discharged on the eighteenth hospital day in good condition.

Laboratory Examinations.—Spinal fluid was clear. Pandy test was negative; Wassermann test negative. Glucose was 87 mg. per 100 c.c.; protein 26 mg. per 100 c.c.; red blood count 5.22; hemoglobin 79 per cent; color index 0.75; white blood count 22,560; platelets normal; differential

A. *B.*

Fig. 1.—Prostigmine test. *A*, Before; *B*, thirty minutes after administration of Prostigmine.

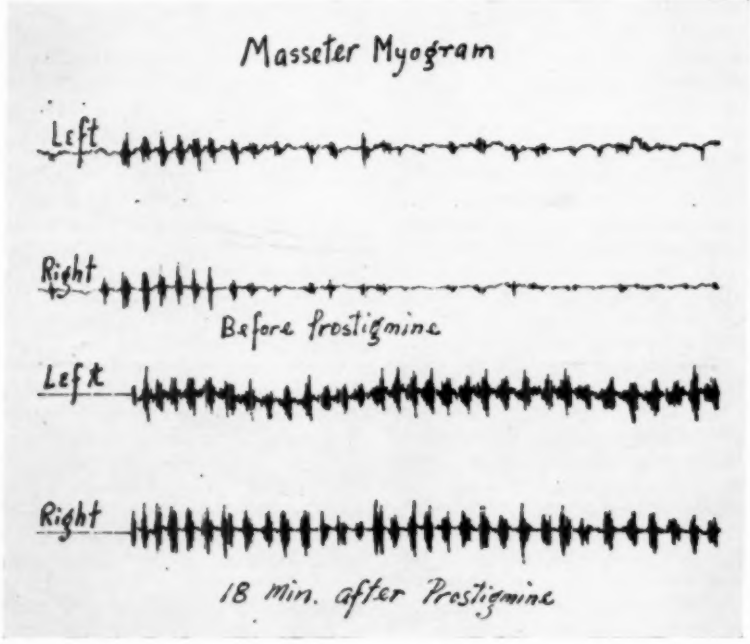


Fig. 2.—Electromyogram of masseters. *A*, Before, and *B*, after Prostigmine.

—neutrophils 51 per cent; bands 39 per cent; lymphocytes 6 per cent; monocytes 4 per cent; few Döhle bodies. Blood chemistry: nonprotein nitrogen 34 mg. per cent; glucose 110 mg. per cent; potassium 19.9 mg. per cent or 5.1 meq. Urine was normal. X-ray of heart and lungs was within normal limits. There was no evidence of thymic shadow. The skull showed no evidence of osseous pathology, and no abnormal calcifications or evidence of increased intracranial pressure. There was no evidence of lead lines in long bones, and no osseous or intra-articular pathology.

Electromyogram.—Surface electrodes were paired and applied to both masseters. The patient was given gum to chew. Initial voltages were low and myasthenic response was noted in 13 seconds. Prostigmine was given intramuscularly and records obtained at 12- to 2-minute intervals. The records revealed increased voltage and prolongation of fatigue time to about 50 seconds (Fig. 2).

Electrical Stimulation.—There were brisk response of all muscle groups of all extremities to galvanic current and slow response to faradic current.

Psychological Evaluation.—Since the patient at 10 years of age was only in the third grade of school, two years behind the normal grade, we inquired about his school record.

The psychological tests made at the Board of Education showed the following results:

First test—Thurstone Scale—done Dec. 11, 1947.

Chronological age: 6 years 11 months.

	Perception	*Quantitative*	*Motor*	*Space*
Factor age	4.7	3.0	5.5	3.3
Factor quotient	66	43	81	47

Second test—Revised Stanford-Binet, Form L, done on Nov. 28, 1949.

Chronological age: 8 years.

Mental age: 5 years 1 month. M.A. Expectancy: Kindergarten.

I.Q.: 64. Very slow rate of mental growth.

On Oct. 17, 1951, the psychological test was repeated at the Dr. Julian D. Levinson Research Foundation. The Stanford-Binet intelligence test, Form L, was given two weeks after the patient's discharge from the hospital. The results of the test were as follows:

Chronological age: 10 years 9 month.

Mental age: 6 years 2 months.

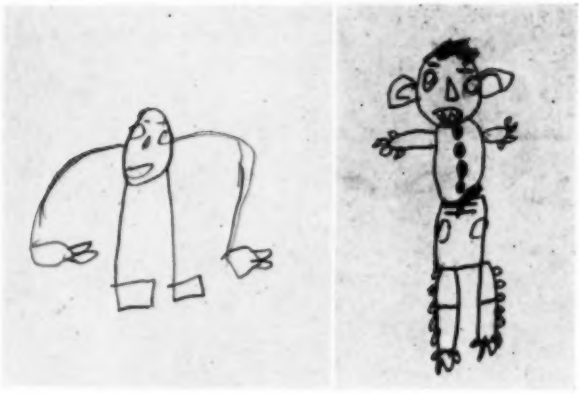
I.Q.: 57.

After 6 months of Prostigmine, the I.Q. showed a change from 57 to 81. There was also great improvement in the Goodenough test (drawing of a man) (Fig. 3).

On the Bender Motor Gestalt test, taken after the administration of Prostigmine, the boy's ability to copy figures was greatly improved. There was an increase in speed and better comprehension. The ability change one hour after Prostigmine was from maturation age 5-9 to 6-3 (Fig. 4).

The patient was readmitted to the hospital on June 8, 1952, with a history of cold, cough, and anorexia. The day before admission the patient developed a fever. Oral temperature was 103° F. on admission, respiration 20, pulse 120. Skin was clear. There was bilateral ptosis, more marked on the left; pupils reacted to light; conjunctivae were pale; ears, nose and throat were negative. There was slight bilateral cervical adenitis. There were moist, bubbling râles throughout both lung fields. The heart was normal except for a tachycardia. Abdomen was negative; extremities long and thin. There was generalized weakness. Genitalia negative.

Hemoglobin on day of admission was 82 per cent; red cell count 5.55; color index 0.73; white cell count 36,000; polymorphonuclears 68; bands 10; eosinophils 1; lymphocytes 15; monocytes 6; sedimentation rate 30



A. *B.*

Fig. 3.—Goodenough (draw a man) test. *A*, Two weeks after Prostigmine therapy. *B*, Six months after Prostigmine therapy.

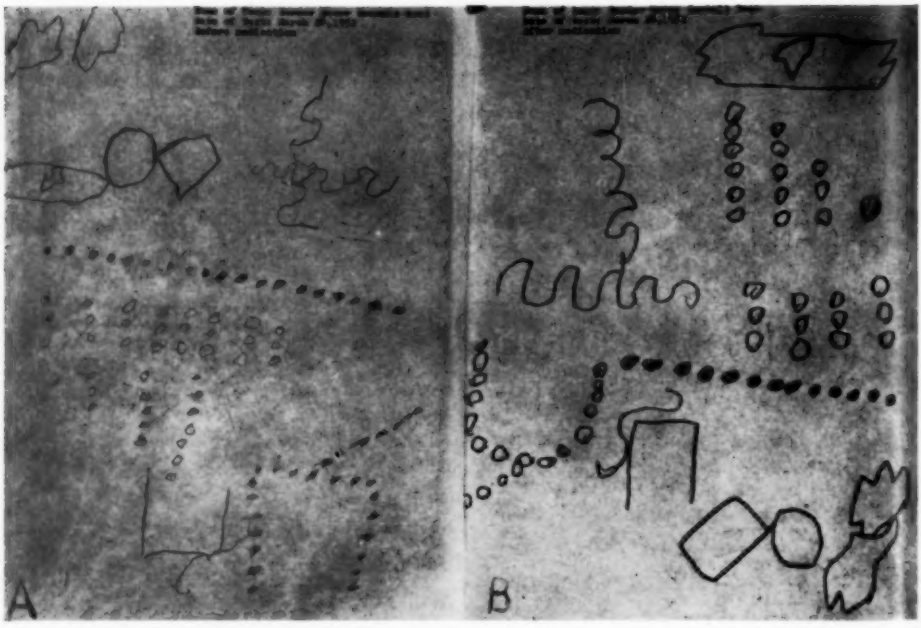


Fig. 4.—Bender Motor Gestalt test. *A*, Before Prostigmine. *B*, After Prostigmine.

mm. (corrected); hematocrit 45 per cent; Kahn test negative. Two weeks later the laboratory findings were: hemoglobin 75 per cent; red blood cells 4.55; color index 0.93; white blood cells 7,000; polymorphonuclears 42; bands 4; lymphocytes 41; monocytes 13.

The total blood protein was 7.3 mg. per 100 c.c.; chlorides 100 meq.; potassium 4.9 meq.; carbon dioxide 44 mg. per 100 c.c. On June 9, 1952, the day after readmission to the hospital, x-rays showed a shift of the mediastinal structures to the right. The left lung field was not involved. In the lower right lung field there was a nonhomogeneous area of increased density, which in the lateral view appeared to be made up of an atelectatic middle lobe. There were infiltrations in the left lower lobe as well. Mantoux test 1:10,000 was negative.

Shortly after admission, the child was given 1.0 c.c. of 1:2,000 Prostigmine. Immediate improvement followed. The patient was able to sit up, to walk and to talk. Five hours later, the bubbling râles began to subside. The patient was put into an oxygen tent and given Prostigmine 1:2,000 every eight hours intramuscularly, streptomycin 0.5 Gm. every six hours and procaine penicillin 300,000 units every morning. The day after admission, a 5 x 35 bronchoscope was passed through a No. 12 laryngoscope. Moderate to large amounts of mucopurulent grayish secretions were aspirated from the bronchi. The following day the findings were much the same but the patient showed some improvement. A day later, the improvement was quite marked. There was no atelectasis or extensive bronchial involvement. On June 20, 1952, twelve days after admission to the hospital, oral Prostigmine was begun. The following day the patient began to vomit and the Prostigmine was cut down to 15 mg. every eight hours. A day later he had a convulsion. On the fifth day after the administration of Prostigmine, the patient began to feel much better. He could walk, chew, and count better than before. Ptosis of the eyelids was still present, but to a lesser degree.

The patient was discharged from the hospital in good condition. He was put on Prostigmine, 15 mg. every six hours, and 3/8 grain ephedrine, three times a day.

Six months later, on Nov. 16, 1952, the patient was admitted to the hospital for the third time. He was now 11 years 11 months of age. Mother stated that the boy had complained of a stomach-ache and a few hours later suddenly lapsed into a coma. The patient was comatose on arrival at hospital. Temperature was normal at first but four hours later was 101.2° F. rectally. Pupils were small and equal and did not respond to light. A moderate amount of mucus was found in the pharynx. Slight stiffness of the neck was noted. The pulse was 130 per minute. Coarse râles were present over both lung fields. X-ray of the chest revealed a bilateral bronchopneumonia. Urinalysis was negative.

Immediate treatment consisted of oxygen, constant pharyngeal aspiration, procaine penicillin 300,000 units intramuscularly, and Prostigmine 2 c.c. of a 1:400 solution subcutaneously. The patient expired suddenly, twenty-four hours after admission.

Autopsy revealed the following: Slight hypertrophy of the left ventricle, bilateral bronchopneumonia, bilateral pulmonary edema, bronchitis and hyperplasia of the lymph nodes. It also showed petechial hemorrhages of the colon, hyperplasia of Peyer's patches and solitary lymph follicles of the ileum, fatty and congestive liver and passive congestion of the kidneys. The thymus was normal in size. There were numerous whitish dots throughout the thymus which measured 0.5 to 1 mm. in diameter. The thymus was pale in color and of normal consistency. Microscopically, the thymus was normal. The brain showed marked congestion of the meningeal vessels grossly and microscopically.

DISCUSSION

According to Guthrie,[11] Willis was the first to describe myasthenia gravis in 1685 and Sir Samuel Wilks recorded a case in 1877.

This disease has been called by various names: bulbar paralysis without discoverable anatomical changes, asthric bulbar palsy, Ebb-Goldflam, Hoppe-Goldflam symptom complex, and myasthenia gravis pseudoparalytica.

Myasthenia gravis was thought to be more common in the male. However, of 125 adult cases studied by Harvey,[12] 57 per cent were female and only 43 per cent were male. Harvey found the greatest number of cases occurring during the second, third, and fourth decades of life.

Because of the greater and better diagnostic facilities, even transient neonatal myasthenics born of myasthenic mothers have been recognized of late. The symptoms, manifested shortly after birth, are masklike facies, weak cry, ptosis, weak swallowing reflex, and even collapse if therapy is not instituted early. Levin[13] stressed the fact that in congenital myasthenia the muscle involvement is bilateral. There is also a history of delayed quickening. The symptoms appear immediately after birth and the fetal movements in utero are weak. The mother, Levin says, should be studied for possible latent myasthenia.

The question of heredity is still a debatable one. However, there is some evidence that points to heredity as a factor. Riley and Frocht[14] report two cases in sisters, Rothbart[15] four cases in brothers, Bowman[16] mentioned two cases in cousins, and Levin[13] reported two cases in siblings.

Potassium concentration in both the muscle and serum is considered to play a very important part in the onset of fatigue.[17] Normally, the intracellular component of muscles contains 80 meq. per liter of potassium per kilogram and the serum 4 to 5 meq. per liter. If this ratio is disturbed in either direction, muscular weakness results. When the myasthenia gravis improves, the muscle potassium, according to Cumings,[18] approaches normal with corresponding clinical improvement. In our case, the potassium was normal.

The thymus was first implicated in myasthenia gravis in 1901 when Wiegart[19] published a case associated with thymic tumor.

In 1908, Booth[20] described a case of myasthenia gravis in an 11-year-old child, who, on autopsy, showed no anatomical changes except for a slight enlargement of the thymus. He, however, explained the symptom complex on the basis of nutritional disorder impairing the muscle function caused by an unknown toxin. Since that time, a relation was found, by several authors, between myasthenia gravis and thymic pathology.[21, 22] For these reasons, surgical removal of the thymus has been done in many cases of myasthenia gravis.

The central and peripheral nervous system show no changes in myasthenia gravis. In our case, there was no pathology of the central nervous system outside of engorgement of the blood vessels in the brain.

Since the ptosis due to paresis of one or more of the extraocular muscles is among the earliest manifestations of the disease, about 50 per cent of the myasthenic cases are seen first by an ophthalmologist.[23]

The symptoms of myasthenia may appear either insidiously or acutely. The weakness is increased by fatigue. The symptoms are, therefore, less marked in the morning than in the afternoon or evening. The patient finds it easier to work at the beginning of the day but after several attempts he becomes fatigued. The patient may complain of double vision or of inability to open his eyes well. Chewing may not be difficult at the beginning of the meal but soon becomes so because of fatigue of the muscles of mastication and deglutition. Water may even be regurgitated through the nose. Words that may have been spoken distinctly at first soon become muffled and inaudible. If the muscles of the face are also involved, the face becomes masklike and the lower jaw drops. Muscles supplied by the "bulb" are the ones frequently involved. Any group of muscles may be affected. The clinical picture varies in different cases. Any unexplained fatigue that is relieved by rest should make one suspect a myasthenia gravis, unless proved otherwise by a Prostigmine test.

We should like to point out the special points of interest in the case of myasthenia gravis reported by us.

1. The early onset: the patient was only 9½ years of age when the myasthenia was discovered.

2. A differential diagnosis had to be made between myasthenia gravis and bulbar poliomyelitis.

3. The question arose as to whether the pneumonitis was due to a weakness of the muscles of the chest wall and diaphragm. The fact that the pneumonic symptoms cleared up in a few hours indicated that it was not a real pneumonia and that the myasthenia was in some way accountable for the condition. On the final admission to the hospital, however, the patient had a definite bronchopneumonia, which was confirmed by necropsy.

4. The myasthenia gravis in our case was associated with mental retardation. The question arose as to whether the two were interrelated or were separate conditions. Since most patients with myasthenia are not retarded, we regarded each as a separate entity.

5. A comparison of the I.Q. with other psychological tests shows that the verbal I.Q. is not a fixed measure of basic intelligence, and should be done in conjunction with other tests.

6. When Prostigmine was given, the child became more alert mentally as well as physically, although his intelligence quotient never reached normalcy.

7. The blood potassium was normal all the time.

8. There was no evidence of thymic enlargement on x-ray nor was there any evidence of thymic pathology on autopsy.

9. The brain showed no anatomic changes.

SUMMARY

A 10-year-old male with symptoms of myasthenic crisis presented diagnostic difficulties at first, with particular reference to bulbar poliomyelitis. Subsequent tests, however, proved the case to be myasthenia gravis.

The patient was also mentally retarded as shown by his I.Q. and his performance at school. Under Prostigmine therapy he improved, not only physically but mentally, although he never attained normal mentality.

The patient died a year and two months after the diagnosis was established. Autopsy revealed a bronchopneumonia but no thymic involvement.

Our sincere thanks go to Dr. Rodriguez of the Department of Physical Medicine, University of Illinois, for the electromyogram, and to Mrs. Delilah White, psychologist at the Dr. Julian D. Levinson Research Foundation, for the psychological tests performed on the patient.

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ABDOMINAL EPILEPSY

Report of a Case Controlled With Tridione

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ABDOMINAL epilepsy is a syndrome characterized by sudden, severe, colicky abdominal pains, episodic in occurrence, variable in duration, and usually followed by a postictal exhaustion and sleep. The pain is generally periumbilical but it may radiate to the epigastrium. It is occasionally associated with nausea or vomiting, rarely diarrhea, and is not accompanied by frank clinical convulsions or loss of consciousness. There may be pallor, sweating, and clonic movements of the abdominal muscles. The patient may exhibit behavior disturbances, nightmares, and personality changes.

Abdominal pain associated with epilepsy was originally described by John Hughlings Jackson (1835-1911). However, the syndrome of abdominal epilepsy as such was not definitely presented until Moore reported his first case in 1944.[1] Previous to Moore's description, when any cognizance was taken of paroxysmal abdominal pain, it was usually diagnosed as abdominal migraine or an abdominal equivalent of migraine. Thus, Brams[2] in 1922 considered the pain of abdominal migraine as arising in the celiac plexus and its branches. Blitzsten and Brams[3] later wrote that in the "abdominal equivalent" of migraine, the pain and other symptoms may be due to the occurrence of a "storm center" involving the region of the vagus nuclei with transmission of the impulse to the sympathetic system.

The precipitating impulses for abdominal epilepsy arise in the brain. The exact localization of cerebral representation of gastrointestinal activity and abdominal pain has not been definitely established. However, Moore reports that clinical data concerning the effects of brain lesions and experimental stimulation of cortical areas point to areas 6, 5, and 3 of Brodmann and/or the diencephalon as the responsible locations.[4, 5, 6]

Often no etiological background can be ascertained. Yet Moore[4, 5] notes that abdominal epilepsy may be consequent to tuberous sclerosis, brain tumor, brain damage resulting from head injury, and various other causes. He even presents a case of a 32-year-old man with onset of symptoms at 9 months of age as a result of angioneurotic edema of the brain following a diphtheria antitoxin injection. There were cerebral cortical changes demonstrated in the electroencephalogram.

Certain criteria for the diagnosis of abdominal epilepsy may be noted.

1. A history of sudden, episodic, paroxysmal abdominal pain, usually periumbilical or epigastric, frequently followed by exhaustion and sleep.
2. Exclusion of intrinsic visceral disease by adequate examination and laboratory investigation.
3. An abnormal electroencephalogram showing psychomotor disturbance.

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4. Clinical and electroencephalographic response to anticonvulsant drugs.

One of the more constant and, therefore, significant findings in abdominal epilepsy is the abnormal electroencephalogram without a history of head and brain injury. Lambert[7] reports that the cerebral dysrhythmias are of the petit mal and psychomotor equivalent types. In a series of fourteen children with abdominal epilepsy, Livingston[8] found that ten had abnormal electroencephalograms. Furthermore, the abnormalities were present even when the patients were asymptomatic. However, Livingston declares that a normal electroencephalogram does not necessarily obviate the diagnosis of abdominal epilepsy if the history and a therapeutic test validate it. He maintains that the clinical response to anticonvulsant drug therapy is the most important criterion.

Abdominal epilepsy is often misdiagnosed as mesenteric adenitis, colic, hypoglycemia, intussusception, Meckel's diverticulitis, behavior disorder, and even psychoneurosis in adults. Many an unnecessary laparotomy is performed, and many a child is given a needless prolonged course of psychotherapy for this syndrome.

Previous to Moore's discrediting of the diagnosis of abdominal migraine, paroxysmal nonvisceral abdominal pain was frequently treated with ergotamine tartrate with uniform lack of favorable results. The barbiturates also proved ineffective. However, with correct diagnosis, Dilantin Sodium (diphenylhydantoin sodium) was used with good results in the majority of cases. Thus Livingston[8] achieved control of abdominal pains in eleven of his fourteen reported cases.

The following case is presented as one in which Dilantin Sodium produced only transient relief from abdominal pains but where Tridione (trimethadione or 3,5,5-trimethyloxazolidine-2,4-dione) then proved completely effective in eliminating all symptoms, physical and psychic.

CASE REPORT

J. S., a 4-year-old white boy, was first seen on March 23, 1953, with complaints of severe frequent attacks of abdominal pains "in the pit of his stomach," which occurred almost daily, day or night, frequently awakening him from his sleep. The pains were first noted on Feb. 8, 1952, when he woke up screaming during the night. The pains have never been accompanied by vomiting. The stools have always been normal but occasionally have exhibited some mucus.

After a short while, the boy's mother began to note progressive deterioration in his behavior so that he became antisocial, belligerent, withdrawn, destructive, and a severe disciplinary problem in the home. This was quite at variance with his previous usually pleasant behavior.

The mother had an uneventful pregnancy with this child and was delivered at term of a normal infant weighing 6 pounds 13 ounces. The patient had a normal infancy. He walked at 12 months and talked by 2 years of age. Except for a mild case of pertussis at 2 years of age, his health was always excellent. He was the second of four siblings, with a sister 6 years old, a sister 14 months old, and a brother 2 months old. His present illness began a few weeks after the birth of the third child. Later, it was thought to be aggravated when the fourth child arrived. The family relations were quite good. The parents loved each other and the children, although the father was strict

in his discipline. Since the onset of the child's behavior disturbance, there had been frequent clashes between him and his father.

Soon after the onset of the child's symptoms, a gastrointestinal x-ray series was performed and the diagnosis of duodenal ulcer was made. The boy was treated with phenobarbital, belladonna, and Sippy powders for two weeks without improvement. Five days of treatment with Banthine also proved ineffective. Another gastrointestinal x-ray series was done and this time no ulcer or other abnormal findings were reported except possible irritability of the duodenum. The child was then admitted to a large general hospital for study on April 8, 1952.

In the hospital, a careful physical examination revealed no cause for abdominal pain. No distention, masses, or organs were felt, and no hernia was seen. Laboratory findings included normal blood sugar, normal urinalysis, and normal blood count. On a meat-free diet, guaiac test for blood in the stool was negative, and no ova or parasites were found. A gastrointestinal x-ray series was done on April 9. No abnormality was found in the esophagus or stomach. The duodenal bulb was complete and no irritability was noted. The small bowel, studied at short intervals, showed no abnormality in pattern or motility. The terminal ileum appeared to be fully distensible. The large bowel was normal also. Gastric emptying time was within normal limits. X-ray enema studies showed the barium to pass freely from the anus to the cecum without revealing any gross abnormality. The mucosa was well delineated and regular in appearance.

During his hospital stay, the child seemed to be much better than his parents had described. However, on one occasion he did awake at night crying and complaining of abdominal pain. After reassurance, the pain subsided and the child returned to sleep almost immediately. His temperature was normal throughout his period of hospitalization. There was no diarrhea or vomiting. The boy was discharged on May 11, 1952, with the final diagnoses of "(1) behavior disturbance; (2) abdominal pain on emotional basis."

The abdominal symptoms continued and the child's behavior was almost unbearable. Treatment with antispasmodics, barbiturates, and vitamin B complex all failed to help him. Finally, the family was persuaded to accept psychiatric assistance for the boy.

When I first saw the child on March 23, 1953, he was wild, screaming, and unapproachable. Physical examination, including neurological findings and eyeground inspection, was completely normal. The history of paroxysmal abdominal cramps of one year's duration without organic pathology and with marked behavior disturbance suggested the diagnosis of abdominal epilepsy. An electroencephalogram was performed on March 30 and was reported as follows: "Bipolar and monopolar recordings were taken. Moderate voltage, irregular activity, 15 to 20 cycle per second waves in the frontomotor region. Interspersed are random 7 to 8 cycle per second waves more pronounced on the left side. In the parieto-occipital area the waves are irregular 6 to 8 cycle per second interspersed with low amplitude 10 to 12 cycle per second waves. In the frontomotor parietal region on the left side there is a tendency to slower frequency. Moderate amount of alpha activity in the occipital region. Hyperventilation on three occasions resulted in high amplitude, irregular activity with discharges of high amplitude, 3 to 4 cycle per second waves. *Impression:* Abnormal electroencephalogram revealed a psychomotor disturbance with some evidence of petit mal activity." (Fig. 1.)

At a subsequent visit to the office, the child was seen at the end of an attack of abdominal pain. Physical findings were negative except for clonic abdominal muscle spasms. While his mother and the doctor were

conversing, the child fell into a sleep of exhaustion on the floor.

Treatment was started on April 7 with Dilantin Sodium 0.03 Gm. three times a day. There was cessation of abdominal cramps within two days and marked improvement in his behavior. He became tractable and less dependent. However, after 3½ weeks the abdominal symptoms and behavior disturbance began to return and persisted though not as severe as before therapy was instituted. The condition became no better when Dilantin Sodium was given four times a day, with three doses of 0.03 Gm. and a bedtime dose of 0.06 Gm. Therefore, on May 18 Dilantin Sodium was discontinued and Tridione was prescribed, 0.3 Gm. three times a day. There was rapid improvement in all respects and the child has been completely free from symptoms since June 1, 1953. Medication has been continued at the same dosage level and at the time that this paper was written eight months later, the boy was "a joy and a model child" according to his mother. Repeated

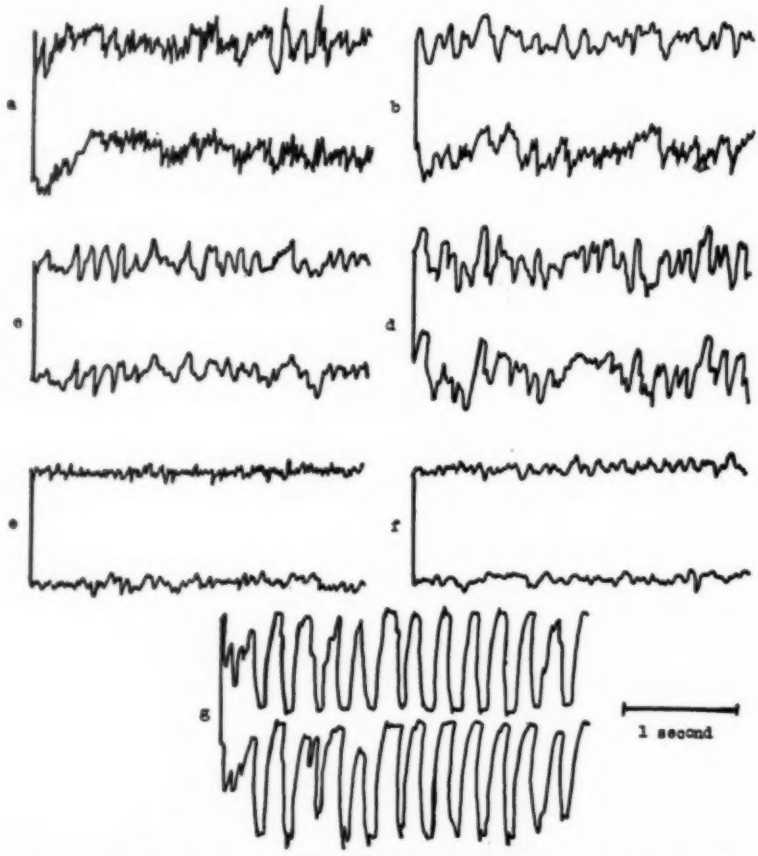

Fig. 1.—Electrocardiogram, J. S., March 30, 1953. *a*, Frontal motor: upper, left; lower, right. *b*, Motor parietal: upper, left; lower, right. *c*, Parietal occipital: upper, right; lower left. *d*, Motor occipital: upper, left; lower, right. *e*, Upper, frontal frontal; lower, motor motor. *f*, Upper, parietal parietal; lower, occipital occipital. *g*, Motor occipital, after hyperventilation: upper, left; lower, right.

blood counts at monthly intervals have all been normal, showing no depressing effects on the hematopoietic system from the Tridione.

COMMENT

Because of its uncommon occurrence, abdominal epilepsy is frequently overlooked. Abdominal pains are such a general complaint in childhood and are often the result of air swallowing, poor bowel habits, overactivity at mealtimes, and so on. Frequently enough, the complaint is malingered or at least exaggerated as to severity or duration where the child feels that he has something to gain by the ruse. In the young child, pains are rarely, if ever, unconscious conversion symptoms. If psychogenic, the pains would probably not persist unchanged for many months. Of course, if abdominal pains are severe and persistent, they must always be investigated in order to establish the presence or absence of organic visceral causation. Where organic etiology has been ruled out, such paroxysmal pains must always lead one to suspect abdominal epilepsy. The electroencephalogram and the therapeutic response to anticonvulsive drugs help to establish the diagnosis.

The case presented above was quite typical of abdominal epilepsy. There was the history of characteristic pain, the antisocial, impulsive behavior disturbance, the absence of organic findings, the positive electroencephalogram, and the therapeutic response to anticonvulsive drugs.

A review of the literature on this syndrome revealed Dilantin Sodium to be the most effective drug in most cases. The present case responded temporarily and incompletely to Dilantin Sodium. Then Tridione was instituted with perfect results. Tridione might be expected to be more effective than Dilantin Sodium with an electroencephalogram showing general psychomotor disturbance and evidence of petit mal activity.

SUMMARY

1. Abdominal epilepsy is characterized by episodic, severe, paroxysmal abdominal pains in the region of the umbilicus and epigastrium.

2. It has its origin in the cerebral cortical areas 6, 5, and 3 of Brodmann and/or the diencephalon.

3. It may be associated with marked behavior disturbances.

4. Criteria for diagnosis are typical history of pains, elimination of organic visceral etiology, positive electroencephalogram, and therapeutic response to anticonvulsive drugs.

5. A case of abdominal epilepsy is presented which showed a temporary and incomplete response to treatment with Dilantin Sodium, but then a prolonged and complete therapeutic response to Tridione.

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TRACHEOCAROTID FISTULA WITH FATAL HEMORRHAGE FOLLOWING TRACHEOTOMY FOR POLIOMYELITIS

A Case Report

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FOR many years tracheotomy has been an accepted surgical procedure often utilized in the treatment of patients with bulbar poliomyelitis who exhibit signs of respiratory embarrassment. The literature contains but few references to fatal complications following tracheotomy, although numerous such operations are performed yearly. It is to focus attention on a real, albeit a rare, complication of this relatively simple surgical procedure that this paper is written. A search of the literature revealed only two similar cases, one reported by Johnson[1] and another alluded to in his article without a reference, the original report of which we were unable to locate.

CASE REPORT

J. M., an 8½-year-old white male, was admitted to Childrens Memorial Hospital, July 27, 1952. The child had been well until July 25, when he had an episode of vomiting. His mother stated that for the prior few days (approximately July 21) she had noticed that he had fatigued more readily but that he had no complaints. On the morning of July 26 the patient again vomited and complained of difficulty in swallowing and shortness of breath. Toward evening he was unable to close the left eyelid, he had paralysis of the right side of the face, and his voice sounded "fuzzy." A physician was consulted and the child immediately sent to the hospital.

The admission physical examination revealed a well-developed and well-nourished cyanotic white male who appeared acutely ill. A pronounced vocal twang was noted, and large quantities of mucus were present in the pharynx. Respirations were labored and almost entirely abdominal. The oral temperature was 102.6° F., the respirations were 46, and the pulse was 100. There was no paralysis of the muscles of the extremities. The patient was immediately tracheotomized and placed in a Drinker-Collins respirator because of the marked respiratory embarrassment and cyanosis. Initial laboratory examinations were as follows: white blood cells 13,600, segmented forms 83, lymphocytes 17; red blood cells 6.80 million; hemoglobin 15.5 Gm.; hematocrit 52; carbon dioxide combining power 41.4 vol. per cent.

During the first six days of treatment the child was extremely restless and uncooperative. It was noted that the diaphragm of the Drinker-Collins respirator caused some motion of the tracheotomy cannula and the tracheotomy tube moved superoinferiorly and rotated laterally to the right with each respiratory excursion. In order to maintain an adequate airway, almost constant suctioning of mucus from the trachea and frequent adjustment of the tracheal cannula were required. By August 10 he had shown considerable improvement and was able to remain out of the respirator for varying periods of time up to twenty minutes.

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Fig. 1.

Fig. 2.

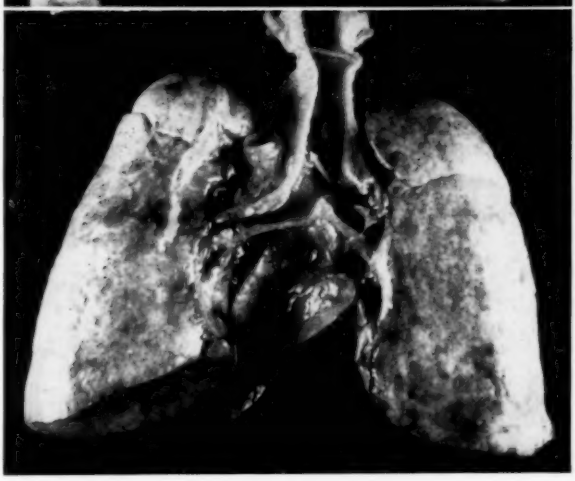

Fig. 1.—Photograph of posterior aspect of respiratory tract with tracheotomy tube in place. Note the tip resting upon the carina.

Fig. 2.—Photograph of posterior aspect of respiratory tract showing tracheotomy stoma at fourth, fifth, and sixth tracheal rings. The arrow marks the site of the tracheal opening of the tracheocarotid fistula.

Eighteen days after the tracheotomy the patient had a spontaneous hemorrhage around and from the tracheal tube. The blood was bright red and gushed from the tube, the nose, and the mouth. Two episodes of vomiting of brownish liquid material occurred. Suction through the tracheotomy cannula was begun immediately and intravenous fluids started. The hemorrhage continued in spite of all efforts to control it, and the patient expired within fifty minutes after the onset.

rested on the hyperemic carina. The tracheotomy tube measured 5.5 cm. along its concave border; the trachea, from the inferior border of the tracheotomy stoma to the carina, measured 5.0 cm. The tracheal mucosa was eroded, markedly injected, and edematous for approximately 1.5 cm. below and slightly to the left of the inferior border of the tracheotomy stoma. In the center of this eroded mucosa there was an irregularly ragged and hemorrhagic aperture, 0.3 cm. in diameter, communicating

Fig. 3.—Photograph of lumen of left common carotid artery. Note the arterial aperture of the tracheocarotid fistula.

Post-mortem Examination. — The thoracic viscera, including the organs of the neck, were removed en masse. The trachea was opened by a posterior approach from the larynx through the primary bronchi. The tracheal mucosa was covered by liquid and semiclotted fresh blood which extended for varying distances into the secondary bronchi and which had occluded the lumens of some of the smaller bronchioles.

A tracheotomy stoma, measuring 1.5 by 1.0 cm., was present from the fourth through the sixth tracheal rings. There was moderate hyperemia of the mucosa over the carina but no ulceration. The tracheotomy tube was reinserted and the tip with the left common carotid artery. The artery was fused to the trachea by firm connective tissue requiring sharp dissection over an area approximately 2.0 cm. superoinferiorly and 1.5 cm. laterally. The channel connecting the artery and trachea measured about 0.5 cm. in length and followed a diagonal course downward and laterally from the trachea.

Microscopic examination of tissue from the central nervous system confirmed the clinical diagnosis of bulbar poliomyelitis. The neuronal elements in the medulla oblongata showed varying degrees of degeneration and neuronophagia. Macrophages, lymphocytes, and a few polymorphonuclear leukocytes were pres-

ent in this area. Many blood vessels, both arteries and veins, showed perivascular cuffing of lymphocytes. The sections of trachea taken from the eroded site and the subjacent areas showed marked polymorphonuclear leukocytic infiltration extending from the mucosal surface into the peritracheal connective tissue. There was complete necrosis of the tracheal mucous membrane, including destruction of a segment of tracheal ring. The trachea and carotid artery were fused by organizing inflamed granulation tissue in which microabscesses were present. The wall of the artery at the site of the aperture was necrotic, but the inflammatory process in the media extended peripherally for only a distance of 1 to 2 mm.

DISCUSSION

The reason for recording this case is not primarily to add the second proved case of a post-tracheotomy arteriotracheal fistula to the literature but to describe the probable mechanism of its pathogenesis. In his report of a similar case, Johnson[1] states that the erosion into the vessel lumen did not occur at the site of the tip of the tube and describes the fistulous tract to be "in the innominate artery, at the bifurcation, with the tear extending into the right carotid artery and slightly into the subclavian." He suggested that the low level of the tracheotomy site (sixth and seventh tracheal rings) and the motion of the tracheotomy tube caused by the sponge rubber collar about the patient's neck are probable factors in the production of the erosion, with secondary artery perforation and subsequent hemorrhage.

In essence we feel that his concept of the pathogenesis is true; however, we wish to call attention to the importance of the length of the tube as it relates to the distance between the tracheotomy stoma and the tracheal carina rather than the respirator movement per se or the low level of the operative site.

It would appear that the lateral rotary movements of the tracheotomy tube causing the tracheal erosion were produced by the upward thrust of the carina upon the tip of the tube. Had the tube been shorter, or the site higher, no such movement could have been induced. Likewise, if the tube had been longer, it would have been fixed in a main bronchus in a lateral position and its motion by respiratory excursions minimized. The actual arterial rupture was undoubtedly produced by the peritracheitis and secondary arteritis which, in effect, produced a localized mycotic aneurysm.

SUMMARY

A case is reported in which there was a massive fatal hemorrhage from a rupture of the left common carotid artery into the tracheal lumen immediately below the site of the tracheotomy. The lesion was initiated by the constant erosive lateral movement of the tracheotomy tube caused by the upward thrusting of it by the tracheal carina.

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TICK PARALYSIS (SUCCESSFULLY TREATED IN THE STAGE OF ATAXIA)

Report of a Case

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TICK paralysis was first described by Howell in Australia in 1824. It was first reported in North America by Todd[1] in 1912. It was believed confined to the Rocky Mountain area in this country until 1938 when Robinow and Carroll[2] described a case in Georgia. Since these original reports, 128 cases have been reported from the northwestern states and about twenty-five from the southeastern and Atlantic Coast states. The disease has been reported from six states of the Rocky Mountain area (Colorado, Idaho, Montana, Oregon, Washington, and Wyoming),[3] one state in the Southwest (Texas),[4] two states in the Northeast (New York,[5] Pennsylvania[6]), and seven states in the Southeast (Alabama,[7] Georgia,[8] Kentucky,[9] North Carolina,[10] South Carolina,[11] Tennessee,[12] and Virginia[13]) as well as the District of Columbia.[14]

The disease first manifests itself as an ataxia of the lower extremities which gradually progresses to involve the upper extremities. The next stage is that of weakness and then paralysis of an ascending type. If still untreated, bulbar signs develop and the patient expires in respiratory failure. The diagnosis is made by discovery of the offending tick and the treatment consists of removal of this arthropod. The central nervous system is presumably affected by a toxin elaborated by the fully engorged pregnant female tick *Dermacentor andersoni or Dermacentor variabilis*[15] approximately ten to twelve days after the attachment. If a patient is first seen in the stage of true weakness—after the cerebellar type picture has disappeared—the diagnosis of anterior poliomyelitis may appear to be the most obvious one. But, if by the simple removal of a tick, a case that appears to be a severe poliomyelitis can be *cured,* a careful search for such an agent would certainly appear to be worth while. In the case here presented the tick was removed during the stage of ataxia which occurs before the development of weakness.

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CASE REPORT

C. S., a 5½-year-old white girl with shoulder length blonde hair, was admitted to the Variety Children's Hospital on Nov. 13, 1953, complaining of headache and inability to walk. She had been well until the previous evening, when she complained of headache. During the night she attempted to walk from her bed to the bathroom but was unable to do so because of "lack of control of her legs." In bed she had no difficulty in moving her legs. After sleeping all that night she was still unable to control her legs in the morning but was otherwise well. She was seen by her private physician who sent her to the Variety Children's Hospital with a diagnosis of possible poliomyelitis.

Physical Examination.—She was a well-developed, well-nourished white female child who appeared the stated

age. She was intelligent and cooperative but somewhat frightened by her inability to walk. The neck was not stiff. The cranial nerve functions appeared to be intact. There was no motor weakness of the extremities and no sensory pathway affection. There was marked incoordination of the heel-to-shin test bilaterally. The child was unable to stand or to walk. Finger-to-nose test was normal on each side. The deep tendon reflexes were present in all extremities and equal. The abdominal reflexes were present. The plantar reflexes were flexor. The only abnormal finding in the general physical examination was the presence of large, tender posterior cervical lymph nodes bilaterally. The blood pressure was 110/70, pulse 100, respirations 20, temperature 100.4° F. The blood count showed a red cell count of 4,600,000 with 12.3 Gm. of hemoglobin. The white cells were 10,700 per cubic millimeter with 2 stabs, 70 segmentals, 25 lymphocytes, and 3 monocytes. The blood sugar was 95 mg. per cent. The VDRL test of the blood was negative. The urinalysis was within normal limits except for a 3 plus acetone. The urinary microscopic examination was normal. No ova or parasites were seen in the stool. The spinal fluid pressure was within normal limits. One white cell per cubic millimeter was seen on microscopic examination, and the cerebrospinal fluid protein was 22 mg. per cent. The x-rays of the skull were normal.

Course in the Hospital.—On Nov. 14, 1953, the finger-to-finger test was very poorly performed although the finger-to-nose test was fairly accurate. The child was unable to grasp objects held in the air and was unable to feed herself. Muscle strength was still normal in all extremities. Vibratory and position senses were normal. The deep tendon reflexes were absent in the lower extremities and diminished in the uppers. At 4:00 in the afternoon of November 14 one of the nurses, while bathing the child, discovered a tick in the left parietal region of the scalp. The nurse was unsure of what to do, but at this moment one of us (I. P.) arrived in consultation, recognized the tick and its possible significance, removed it from the scalp, and sent it to the laboratory. It was identified as a fully engorged female tick of the *Dermacentor variabilis say* species.[16] At this time the child's neurological abnormalities consisted of ataxia, dysmetria, dysdiadochokinesis of all extremities, but no nystagmus was present. There was no weakness or sensory loss and the deep tendon reflexes were diminished throughout. Further history revealed that the child had received an inoculation of diphtheria, pertussis, and tetanus toxoid approximately one week before the onset of her weakness and also that the child had a dog which was severely infested with ticks. The child had been prone to rest her head on the dog's. The diagnosis "tick paralysis" was made at this time.

The child began to improve within a few hours after removal of the tick and by the morning of November 15 was feeding herself and walking, although she still walked on a wide base and had some ataxia of the lower extremities. The ataxia of the upper extremities was almost completely gone. By the following morning the child was completely asymptomatic except for a questionable abnormality of the heel-to-shin test on each side. She was discharged as cured forty-eight hours after removal of the tick. Subsequent examination by her family doctor failed to reveal any residuals.

SUMMARY

1. This is believed to be the first reported case in the state of Florida. It is interesting to note that this case occurred during the month of November. Although summer is the time when ticks are found in temperate zones, in south Florida the year-round subtropical climate predisposes to the continuous presence of these insects. Tick

paralysis may occur throughout the year in this area.

2. This patient was first suspected of having "polio." It is hoped that this case report will focus a little more attention on the existence of tick paralysis—a curable paralysis of childhood.

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Medical Progress

RECENT DEVELOPMENTS IN THE COMMON CONTAGIOUS DISEASES

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DEVELOPMENTS in recent years in the knowledge of the common contagious diseases have largely to do with a better knowledge of the viruses and particularly with how to prevent infections due to them. The decade of the 1940's brought us development of the sulfonamides, and discovery of the powers of the antibiotics, so that most bacterial infections can now be controlled, but we still are helpless before most virus infections once they have developed clinical manifestations. In the prevention of such infections, however, definite progress has been made both with serums and with vaccines. Also, in the bacterial disease of whooping cough, there is better understanding of the use of the vaccine; the skin test for susceptibility to mumps is proving useful, and a newly recognized disease, rickettsial pox, has been described that can readily be confused with chicken pox.

Of the five common virus infections of children, measles, rubella, chicken pox, smallpox, and mumps, the individual viruses are similar in that all strains of each of these viruses are antigenically similar. In each disease one cannot distinguish by serological means between strains of virus isolated from different outbreaks. Primary infection takes place in the respiratory tract and is followed by a long incubation period. These diseases are blood-borne infections in which the virus spreads in the blood stream so as to reach the tissues where the characteristic lesions develop. Antibodies are formed which neutralize the virus, that is, in their presence the virus cannot infect cells. These antibodies usually persist for many years if not for life, so that true second attacks of these diseases are very rare.

Influenza and poliomyelitis are similar infections to the above in running a rapid course usually followed by elimination of the virus, but there is little or no cross immunity between types of the same virus so that theoretically at least, second attacks may occur at any time without any modification by a previous attack. The influenza virus can spread on the surface of the respiratory tract without coming in contact with antibodies in the blood stream so that clinical manifestations can develop despite these antibodies. Similarly the poliomyelitis virus can survive and grow in the alimentary canal despite antibodies in the blood stream.

In general, infection with living virus confers a better and longer last-

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Read before the New Orleans Graduate Medical Assembly, March 8, 1954.

ing immunity than does vaccination with killed virus. We have living but attenuated virus vaccines against smallpox, yellow fever, rabies, and various animal diseases, all granting immunity about equal to the actual disease, and we have killed virus vaccines against influenza A and B, certain encephalitides, also rabies, and other animal infections, but the immunity conferred by this group usually lasts not more than six to twelve months. And now it looks as though we have a killed virus vaccine against poliomyelitis.

In general, the common virus diseases of childhood have an essentially normal blood count, rarely over twelve or thirteen thousand white blood cells; also, with the exception of influenza, they have longer incubation periods than do the bacterial diseases such as diphtheria, scarlet fever, and whooping cough, and they are more contagious even than whooping cough. While today we have a cure for nearly every bacterial infection, we have none except time and the forces of nature for practically all the virus diseases, except perhaps those caused by the largest viruses such as psittacosis and trachoma.

Some of the virus diseases can be prevented temporarily by the antibodies present in the gamma globulin fraction of human blood, particularly measles and infectious hepatitis, and perhaps rubella, mumps, and poliomyelitis.

Gamma globulin is always given intramuscularly. It is about one-twenty-fifth the volume of whole plasma, and it is free from the virus of serum hepatitis. After a syringe has been filled with gamma globulin the injection should be made at once, otherwise the piston is likely to become frozen in the barrel of the syringe.

In the prevention or modification of measles, the value of gamma globulin has its greatest certainty, and, regardless of the demands for other purposes, particularly poliomyelitis, enough gamma globulin should be allocated to measles so that any doctor who wants to protect any patient of any age who has been exposed to measles anywhere should be able to get the necessary serum. In New York City at least, probably elsewhere, a doctor cannot obtain gamma globulin to prevent measles except for children 6 months to 5 years of age, for pregnant women, and for people already ill. He cannot obtain it for children 6 years of age and over no matter where exposed.* But many of us feel very strongly that any susceptible person who has been definitely exposed should be given at least a small or modifying dose of the serum, no matter how old or where exposed. A full case of measles is always uncomfortable and occasionally very serious due to such complications as measles encephalitis.

Measles is not a special danger to pregnant women but rubella or German measles is a very serious danger to the fetus if the mother contracts the disease in the first ten to twelve weeks of the pregnancy. Accordingly, women with early pregnancies who have been exposed to rubella should be given 12 c.c. of gamma globulin as soon after the exposure as is practical. The actual protective value has been questioned, but the

*Since this paper was presented, the specific restrictions as to place of exposure and age of child have been removed.

psychological value of such an injection is great.

Infectious hepatitis may spread by direct contact through a family or a classroom. The older the person the more serious the infection may become. Exposed persons would do well to be given 1 to 2 c.c. of gamma globulin. As a matter of fact, 0.01 c.c. per pound is apparently enough to give protection.

The usual gamma globulin is of no proved value for mumps, but if it is prepared from the blood of convalescent mumps cases, as the Army was able to do in World War II, it is of value at least in cutting down the incidence of orchitis from a usual percentage of 25 to 28 per cent in soldiers with mumps to about 8 per cent.

The skin test for susceptibility to mumps has value. The material used is a suspension in saline of mumps virus that is grown on embryonated chicken eggs and then inactivated by ultraviolet light. For the test 0.1 c.c. is injected intracutaneously and twenty-four hours later an area of redness over 1.5 cm. in diameter indicates a previous infection with the mumps virus, and presumptive immunity.

Uncomplicated cases of mumps develop a positive skin test quickly, often in five days. Complicated cases are slow to develop both antibody and skin sensitization, and if a skin test remains negative, gamma globulin may be beneficial.

The skin test is also useful in diagnosis. A positive test at the beginning of a parotitis indicates that the patient is already immune to mumps and the cause of the parotitis is something else. An illness, such as an encephalitis, that is accompanied or followed by a change from a negative to a positive test must have been due to the mumps virus. A father who is being exposed to a child with mumps is vulnerable if he shows a negative skin test, but reasonably immune if his test is definitely positive.

As for gamma globulin and poliomyelitis, injections of 0.14 c.c. of gamma globulin per pound are of only equivocal value in preventing infection with the poliomyelitis virus.

Siblings of a child with polio are forty times as likely to be infected as other children in the locality, but most family infections are contemporary. Therefore, the administration of gamma globulin to siblings is usually too late to give appreciable protection. There is no evidence that gamma globulin given after the onset of symptoms of poliomyelitis has any beneficial effect. And mass injections are exceedingly expensive because in an average epidemic, experience has shown that two thousand children must be injected at a cost of approximately $28,000 in order to lower the incidence by one paralytic case.

Probably the best indications in poliomyelitis for the use of gamma globulin are for small communities such as a summer camp that has been exposed to an actual case, and for known susceptible persons in the presence of an epidemic, such as pregnant women, children unduly exhausted by fatigue, those who must have a tonsil operation or an injection of whooping cough vaccine, and those already sick, especially with a respiratory infection.

The amount commonly given a 50 pound child comprises all the gamma

globulin obtained from a pint of blood. The increase in antibodies is usually not measurable.

The best hope at present for the prevention of poliomyelitis lies in the stimulation of the formation of antibodies in a person's serum by a vaccine. The situation is complicated by the fact that there are three antigenically different types of polio virus: type I, the Brunhilde type; type II, the Lansing type, and type III, the Leon.

Type I is responsible for most epidemics; type II for many subclinical infections; type III causes only about 5 per cent of epidemics. Cross protection is not known.

Two kinds of poliomyelitis antibodies have been identified. First, complement-fixing antibodies, which are comparatively temporary, do not necessarily indicate immunity, and are not entirely type-specific. Second, neutralizing antibodies, which are type-specific, probably indicate immunity to the disease, are comparatively long lasting, and can be developed both by natural infection and by the administration of a vaccine. Neutralizing antibodies are used for establishing the presence of poliomyelitis virus and for identifying the type. In the general American population, 60 per cent of children 6 to 8 years of age, that is, first, second, and third graders, show no antibodies to any type, and only 5 per cent have all three types. Fifty per cent of adults 18 years and over show neutralizing antibodies to all three types. Thus antibodies are naturally acquired as increasing age provides more opportunities for exposure and infection.

It is possible that the amount of antibody necessary to protect against infection is too small to be detected by present laboratory means. (The amount of neutralizing antibody formed by an actual case of poliomyelitis averages an amount which is indicated by a dilution of 1 to 512.)

The requirements of a polio virus vaccine are that:

1. It be effective clinically against all three types.
2. It be long lasting in effect.
3. It can positively be killed.
4. It can be producible in bulk.
5. It contain no pathogenic agent, such as another virus.
6. It contain no allergenic or other harmful agent.

In addition, if not killed but attenuated or modified:

7. It be unable to cause paralysis.
8. It be unable to mutate; to change in virulence.
9. It be unable to infect others if excreted.

Neutralizing antibodies against all three types of polio virus can be formed by the injection of Salk's saline, trivalent, killed poliomyelitis vaccine. The booster response of an injection given in the presence of even only a little antibody raises the level to considerably above the level of antibody that follows an attack of the disease.

For the experimental use this year this vaccine is being distributed in 10 c.c. vials and the injections will be three in number, the second a week after the first, and the third or booster dose, four weeks after the second.

It is not known conclusively but is believed that the presence of neutralizing antibodies which have been augmented by injections of a vaccine

constitutes immunity to infection with the polio virus.

Vaccines for the prevention of whooping cough have been used for years, having been first listed in *New and Nonofficial Remedies* in 1914. The method of preparation, the contents of the product, and the immunizing result were variable for years, but in the early 1930's Sauer and others demonstrated that only recently isolated strains of *Hemophilus pertussis* in Phase I were antigenically potent, although variably so, and from then on whooping cough vaccines became generally used. Two types of preparations have been recently available. The first was a saline-suspended or so-called aqueous vaccine of which a total dosage of 80 billion bacilli divided in three doses and given subcutaneously was recommended. The second was a vaccine treated with an adjuvant, either alum-precipitated, or aluminum-hydroxide-adsorbed, of which a total dosage of 40 billion bacilli divided in three doses and given intramuscularly was preferred for infants. However, there was no suitable standard of potency for these vaccines, and although used widely in the last fifteen years or so with a dramatic effect in lowering the morbidity and mortality of the disease, the vaccines protected completely only about 85 per cent of those injected. However, in those who failed to obtain complete protection, the manifestations of the disease were usually mitigated.

In 1948 a mouse protection test for standardizing pertussis vaccine was adopted by the National Institutes of Health and by the biological manufacturers. The potency was tested by immunizing mice under standard conditions and then in a few days challenging them by the intracerebral injection of exact doses of living pertussis bacilli known to be virulent. The amount of test vaccine required to protect 50 per cent of the mice was compared with the amount required of a standard reference vaccine originally tested for demonstrable protection of children in field trials. As an index of potency the "protective antigenic unit" was developed, the value being determined on the basis of the relative mouse-protective (or $E.D._{50}$) values of the test vaccine compared with the reference standard.

Therefore, beginning in 1953 the potency of all newly prepared whooping cough vaccines must be expressed in terms of "antigenic units," and the total dose of any preparation is 12 units. The amount of the reference standard vaccine that contains 12 protective units contains 96 billion pertussis organisms. Fluid vaccines on the market must contain the 12 antigenic units in the total recommended dose and these units must be provided by no more than 96 billion organisms. Alum-precipitated vaccines, being more antigenic, are limited to 48 billion organisms in the same total dosage of 12 antigenic units.

Whooping cough vaccines, whether saline-suspended, alum-precipitated, or aluminum-hydroxide-adsorbed, may be obtained by themselves, or mixed with diphtheria toxoid alone, or mixed with both diphtheria and tetanus toxoids. The triple mixtures are in general use, those with an adjuvant being advised when the injections are started in infants well under 6 months of age. The latter

should be given intramuscularly to lessen the small danger of sterile abscesses or alum cysts. When the injections are started after the sixth month, the fluid preparations may be preferred and may be given subcutaneously or intramuscularly. Protection in older infants and children may be much more rapid if fluid vaccine is given than if an adsorbed vaccine is used, but in young infants the immunizing response is greater and more lasting following an adjuvant. When aluminum hydroxide instead of alum is used as the adjuvant, the actual injection of the vaccine appears to be less painful.

For almost all preparations now available, the dose is 0.5 c.c. given three times at intervals of at least a month. This provides a total of 12 antigenic units. Single recall or "booster" injections of 0.5 c.c. each are recommended one year after the completion of the first series, again two years later, and two more at three-year intervals, or a total of four boosters in the first decade of life. Whether to continue the injections thereafter is debatable. The degree of immunization obtained may be determined by the pertussis tube agglutination test.

The parents should be warned about the possibility of reactions. Local reactions consist of redness, tenderness, and induration of varying intensity. A nodule may persist for some time at the site of injection. In children over 2 years, there may also be systemic reactions of fever and malaise, but sensitization to foreign protein or susceptibility to the Arthus phenomenon need not be feared. Local reactions should not be treated with heat, either dry or wet, but preferably by quiet, and if the reaction is very severe, cool wet dressings will be found comforting. When an injection is followed by an unusually severe local reaction, the dosage for the next injection should be decreased or the injections discontinued.

Whooping cough vaccine has caused convulsions, possibly as a result of an allergic mechanism, and a damaging, even irreversible, encephalitis has occurred. This complication has usually been after a second or third injection but may follow the first. Hence the administration of any whooping cough vaccine involves a definite but remote risk of serious results. However, the mortality of whooping cough can be so high and the protective value of the vaccine so well established that the truly remote risks should not interfere with widespread use of the vaccine.

To minimize the dangers, one should postpone injecting a child who is in any way ill, give no two injections at the same site, and discontinue the vaccine for any child who developed a high fever from a previous injection, or any allergic reaction, especially a convulsion.

For severe whooping cough, especially in early infancy, the administration of 2.5 c.c. of gamma globulin prepared from the serum of hyperimmunized human beings and given intramuscularly in the buttocks every other day for three doses, has appeared to be definitely beneficial. A fourth dose may be necessary after five to seven more days.

There is as yet no certain specific chemotherapy or antibiotic preparation effective against infection with

H. pertussis. Of the antibiotics in clinical use, the broad-spectrum preparations, Chloromycetin, Aureomycin, and Terramycin, while having the best in vitro effect on *H. pertussis,* have little proved beneficial effect on the manifestations of the disease other than to lower the incidence of secondary infections. This factor, however, makes the administration of one or another of these remedies definitely indicated for all infants with whooping cough, and some authorities advocate giving penicillin also, particularly to the infants.

A recent number of the *British Medical Bulletin,* No. 3 for 1953, contains a symposium on viruses and virus diseases by an eminent group of English scientists. They have studied smallpox very carefully, and have noted that the virus can be isolated from the blood during the early stages of the disease but not after the second day of fever, except in cases which are to prove fatal. The infection can be transmitted from the mother to the fetus in utero usually about the time of the onset of clinical illness in the mother. On the other hand, epidemic evidence suggests to these English authors that most cases of smallpox are not contagious until about the time of appearance of the skin eruptions.

For the diagnosis of smallpox they feel the most reliable test is culturing blood, or smears from skin lesions, on the choreo-allantoic membranes of 12- to 14-day-old chick embryos. The result of the test can be learned in two to three days. A microscopic examination of smears carefully prepared from lesions in the papular or vesicular stages and properly stained can give a high percentage of positive results in as short a time as half an hour.

Of special interest is their observation that convalescent serum added to a suspension of smallpox virus renders the virus incapable of infecting the chick embryo, and they suggest that gamma globulin, particularly if prepared from the blood of immune people, which is most of us, might well be given in the incubation period to unvaccinated contacts of smallpox patients.

Vaccination can also cause a viremia even to the extent of infecting the young fetus in utero so that unless exposed to smallpox, women in the first trimester of pregnancy should not be vaccinated. There seems to be little if any danger to the fetus in the last six months of prenatal life. Schick, however, has reported the very interesting finding of some forty infants who were born pock-marked at full term and of mothers who had been immunized before conception but who during the pregnancy were exposed to smallpox.

People with taking vaccinations are definitely contagious, particularly to infants with eczema. Of course, children with skin eruptions should not be vaccinated, but neither should the healthy clear-skinned siblings of eczematous babies. Vaccinia-immune gamma globulin has been suggested for the treatment of eczematous babies who have been infected by vaccinia.

Both chicken pox and smallpox, particularly the mild form of the latter, known sometimes as alastrim, can be confused with a recently recognized infection now named rickettsial pox. This is a domiciliary dis-

ease entity which was identified in 1946 in Brooklyn by the staff of the Bureau of Preventable Diseases of the New York City Department of Health. It is caused by infection with *Rickettsia akari* and is transmitted to house mice and man by the bite of the blood-sucking mite, *Allodermanyssus sanguineous*. This tiny mite when empty of blood is about 1 mm. in diameter and colorless, but when engorged with blood is red and much larger. Its host in nature is the house mouse and it is also found on the walls of dirty cellars where garbage and other food for mice are allowed to accumulate.

Since 1946, from 50 to 150 cases a year have been reported in Greater New York City, and recently eight cases in one small apartment house in Hartford, Connecticut, and four in Philadelphia have been noted.

The clinical manifestations of the disease have three features. One is the primary lesion at the site of the insect bite; this is at first a firm red papule, which grows to 1 to 1½ cm. in diameter. A vesicle forms in the center, then shrinks and dries, forming a black scab which after about three weeks falls off, leaving a small scar. The lesion is not tender and does not itch. The regional lymph nodes normally become enlarged but are only slightly if at all tender.

Second are the constitutional manifestations which occur about four to seven days after the bite: the patient suddenly develops considerable fever, chills and sweats, headache, backache, malaise, and often photophobia. These various manifestations persist about a week and gradually clear up.

Third is the rash. An eruption appears one to four days after the onset of fever. It is usually generalized in distribution without a pattern, except that, like chicken pox, it is unusual on the palms and soles, and again like chicken pox, lesions have been seen on the tongue and palate. The pocks are discrete, begin as maculopapules, and develop vesicles on top which dry and form small scabs which in turn fall off and leave no scar. The course of the pox is four to seven days in duration, and there are no subjective symptoms due to the eruption. There is usually a moderate leukopenia. There have been no complications and no deaths. There is no specific treatment indicated but Aureomycin, Terramycin and Chloromycetin apparently are beneficial.

Severe chicken pox in the adult may closely resemble rickettsial pox, both diseases having prolonged and distressing eruptions, except that while in chicken pox the vesicle replaces the papule, in rickettsial pox the papular element of the lesions remains throughout, the vesicles surmounting the papules. Search should be made for the primary lesion of rickettsial pox and complement fixation tests can prove this diagnosis. A history of exposure to chicken pox is, of course, important, or, on the other hand, the recognized presence of house mice and of unsanitary conditions can be significant.

The Weil-Felix reaction with Proteus OX19 which is positive in such other rickettsial diseases as typhus fever, both epidemic and endemic, and in Rocky Mountain spotted fever (neither of which has vesicular lesions) is negative in rickettsial pox.

So much for the progress of the recent past. What of the future? This summer should tell us whether or not polio can be prevented. The prospect is so good that a doctor friend of mine who works for the National Foundation for Infantile Paralysis actually is feeling economically insecure and, at the same time, jubilant, due to his belief that conquest of the disease is at hand. Even so, if the polio vaccine is good, it will, of course, take years to immunize enough people to curb that disease and to keep it curbed, and, furthermore, there are in the United States 1,800 people now living in respirators who will continue to need care for many years to come. Similarly with other diseases, smallpox will continue a menace as long as there are people who oppose compulsory vaccination, and there is nothing now known that will stop chicken pox. But progress in recent years being what it has been, we can truly look forward hopefully to dramatic advances in the prevention and cure of most, if not all, of even the virus diseases.

Psychologic Aspects of Pediatrics

PSYCHOLOGIC ASPECTS OF DIETARY DEFICIENCY STATES

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THERE is a sizable group of diseases, often referred to as the psychosomatic disorders, in which the clinical picture is influenced to a greater or lesser degree by emotional factors. Such diseases in children are asthma, certain skin disorders, and ulcerative colitis.

This brief review presents an example of the opposite type of relationship, namely, the influence of altered somatic states (in this case various dietary deficiencies) on psychologic functioning.

SEMISTARVATION

The literature, old and new, contains many accounts of the behavior of persons under famine conditions.[1] As the food supply diminishes the involved persons become more and more preoccupied with food. Food becomes the principal subject for thought and conversation. Coherent and creative thinking is impaired. Energy and thought are directed more and more to finding ways of getting food, and, after a time, the major part of the waking hours are spent in this way.

Other normal activities are reduced or eliminated. Sex interest declines or becomes extinct. The increase in the number of women offering themselves for prostitution is a reflection of the desperation with which food is sought and, at the same time, of the lowering of moral restraints.

In groups affected by famine the usual social amenities are dropped, responsibility to family and loyalty to friends disappear, the incidence of thievery and crimes of violence rises. Riot and rebellion are increased by mild food deprivation, but severe deprivation makes for relative tractability.

During rehabilitation from starvation, the recently starved man is likely to maintain his anxiety about food. Many continue to steal, hide, and hoard food. In contrast to the spiritless, hopeless attitude during starvation, complaints become fierce, bitter, and resentful.

Blanton[2] studied the psychologic effects of undernutrition in the school children in Trier, Germany, during World War I. Forty per cent of the children were suffering from undernutrition to the extent that nervous energy was reduced. The incidence of neurosis, psychosis, abnormal "nervousness," organic nervous disease, tics, or conduct disorders was unchanged. The number of children considered to be borderline defectives rose slightly. The incidence of stuttering was unaffected, but the number of children with lisping, slurring speech was greatly increased. School performance

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was reduced all along the line, and the percentage of children failing to pass their grades at school was doubled. The children seemed to lack energy and interest in their work. They were inattentive, and comprehension of school tasks was poor and slow. Memory was also adversely affected. In addition the children showed a nervous restlessness. Blanton estimated that about 5 per cent of the school population suffered injury to the nervous system of such a nature as to affect the intelligence permanently.

During the famine of 1921 in Russia the starved children manifested a combination of unusual vindictiveness, marked hyperirritability, and chronic crying. Many showed frequent spells of extraordinary rage, animosity, and irritability.[3]

Experimental Semistarvation.—Keys[4] and his co-workers studied the effects of experimentally induced semistarvation in a group of thirty-six young men under controlled conditions. The subjects were conscientious objectors during World War II. They were healthy, intelligent, white men from varied socioeconomic backgrounds. Observations were made before, during, and after a six-month period of semistarvation.

No change in general intellectual capacity was found. Everyday performance was, however, markedly affected. Voluntary mental effort was progressively diminished during the period of dietary deprivation. Such activities as reading, conversation, or writing required more effort and concentration than the person was willing to devote to them.

Sensory activity was unaffected; indeed auditory activity actually improved, to return to the control value during rehabilitation. No significant changes were observed in the Rorschach or Rosenzweig frustration tests.

The behavioral changes were fairly uniform and were similar to those reported from natural starvation. Wide individual differences were, however, observed and were accentuated as the semistarvation progressed. After twenty-four weeks on the restricted diet the men, in addition to being emaciated, were quiet, somber, apathetic, and slow in motion. The facies suggested depression and world-weariness. Questionnaires and interviews revealed that the men were depressed, moody, apathetic, mentally dull, and without ambition.

A somewhat surprising finding was the recognition by the semistarved men themselves of irritability which was not evident in their behavior. They explained this on the basis of an inner rage about which they did nothing because it was too much trouble.

Evidence of neurotic behavior was shown by the results of the Minnesota Multi-phasic Personality Inventory, the details of behavior, and the psychiatric interviews. In contrast to their behavior during the control period, the starving men showed the neurosis triad of hysteria, depression, and hypochondriasis. The extent of the neurotic behavior was roughly proportional to the extent of the weight loss.

During rehabilitation there was a gradual return to normality, but the course was not a simple reversal of the changes that had taken place during semistarvation. A striking feature of the early rehabilitation period was the emergence of irritability which had been previously well concealed. For a time the study subjects became more

troublesome than at any other period during the study. Eventually all changes disappeared except for an unusual interest in food, which persisted in some of the subjects for many months or even years.

THIAMINE

Studies on the experimental production of psychoneuroses through restriction of the intake of thiamine have been reviewed by Wilder.[5] Most of the studies were made in state hospitals. With moderate restriction of thiamine intake, both young and older patients declined in tests which stressed speech and manual dexterity. The decline was greater in the older men, possibly because of the greater susceptibility of tissues already partly deteriorated by the aging process. When the restriction was more severe the decline in performance was accelerated and involved general mental efficiency in the majority of the older men. As the dietary restriction continued, faculties involving attention, interest, ambition, and sociability were unmistakably affected. Consequently there was less talking and much less activity. With still more severe restriction mental changes appeared rapidly and were unmistakable; in some instances there were explosive episodes, tantrums, furors, and rages.

Wernicke's syndrome is characterized by ophthalmoplegia, memory loss, confabulation, apathy or apprehension, clouding of consciousness, ataxia, and sometimes coma.[6] The syndrome is observed in alcoholics, in pregnant women with pernicious vomiting, and sometimes in patients after major surgery when glucose is administered. Peripheral neuropathy may or may not be present. The syndrome has been attributed to thiamine deficiency. Other vitamin B deficiencies are probably also present. The lesion is an acute hemorrhagic polioencephalitis superior. Wernicke's syndrome has almost entirely disappeared, presumably owing to the enrichment of bread with thiamine.[7]

NIACIN

Mental symptoms are prominent in pellagra (niacin-deficiency disease) and frequently precede the typical dermatitis and diarrhea. The early symptoms are often considered neurasthenic. They consist of headache, irritability, difficulty in concentration, forgetfulness, restlessness, apprehension, and a feeling of inability for mental or physical effort. Later on symptoms related to cerebral damage appear—memory defects, confusion, disorientation, intermittent delirium, Korsakoff's syndrome, and dementia. Some patients are excited; others are depressed, anxious, apprehensive, or paranoid. Neurological manifestations such as convulsions, incontinence, cogwheel rigidity, irregular involuntary movements, paralysis, and defective sensation may also be present.

Acute deficiency may produce a state of confusional exhaustion, deep stupor, or coma. The sole manifestation of chronic deficiency may be a neurasthenic syndrome. Mental symptoms of organic brain damage persist in many patients after cure of the pellagra, indicating that irreversible damage to the brain has taken place.

Some of the mental symptoms are probably due to associated deficiencies of other members of the vitamin B group.

Niacin has a beneficial effect on the mental symptoms of pellagra, but its

mode of action is not clear. It probably has a specific action in patients who are suffering from deficiency. In the psychosis of pellagra, brain pyridine nucleotide cohydrogenases are depleted. Nicotinic acid amide is a component of the pyridine nucleotides, which are important constituents of a coenzyme system and participate actively as hydrogen transporters in cellular metabolism. These coenzymes for dehydrogenases participate in the changes which take place between the metabolite and the final oxidation by cytochrome oxidase.

A favorable response of mental symptoms to niacin administration is not to be taken as justification for a diagnosis of specific deficiency. Lehmann[8] reported the successful use of massive doses of nicotinic acid in a man with posttraumatic confusional state. The man had been ill for several months. There was no reason, in the man's history or examination, to suspect pellagra. The changes in the patient's condition following treatment were so striking and so prompt that there could be little doubt that they were produced by niacin therapy.

Niacin may produce its beneficial action through a saturation effect that shifts the balance of coenzyme systems involved in cellular metabolism to a new compensatory equilibrium. There is also evidence that niacin improves cerebral blood flow by producing cerebral dilatation, although this has been questioned.

VITAMIN B_6

Except for listlessness preceding the convulsions, no mention is made of psychologic changes in the two infants with induced pyridoxine deficiency described by Synderman and associates.[9] The "pyridoxine-dependent" infant reported by Hunt and co-workers[10] turned out to be mentally defective.

Apathy, somnolence, and irritability have been observed in some adults with experimentally induced vitamin B_6 deficiency.

KWASHIORKOR

Psychologic changes are seen regularly in children with kwashiorkor.[11a, b] This syndrome is generally regarded as being produced by protein deficiency. It is characterized by undernutrition, edema, frequent watery stools, poor appetite, skin lesions, and hair changes. Especially striking is the appearance of the children. They lie quietly with head bent on the chest, legs drawn up, and an expression of utter misery. When disturbed they may, unlike African children in general, submit to examination, seemingly unwilling to make an effort at resisting or they may register their discontent by irritable whining. They rarely cry out or scream like normal children.

VITAMIN C

Psychologic changes are not prominent in subjects who are vitamin C deficient. Weakness and a feeling of fatigue, which became progressively more marked as the experiment continued, were the only manifestations observed during the studies on experimentally induced scurvy by Crandon and associates.[12] The ability to walk and run (aerobic work) was reduced, but the capacity for anaerobic work, as measured by the muscular activity of the forearm with an ergograph, was undiminished.

The irritability shown by infants with scurvy is due, presumably, to the

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The irritability shown by infants with scurvy is due, presumably, to the

pain associated with a slipped epiphysis and subperiosteal hemorrhage.

VITAMIN D

No data are available on the mental state of infants and children with rickets. Many infants with tetany are unusually jumpy and respond to touch, sound, and change of position with increased activity, crying, and, at times, a convulsion. (This is also observed in the newborn infant with tetany). Others, with similarly low serum calcium values, appear calm and placid.

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Comments on Current Literature

EXANTHEMS AND TISSUE CULTURE

WITH the advent of improved laboratory methods, especially those involving the use of tissue culture, a number of clinical entities is being subjected to investigation. In the course of these studies an interesting array of cytopathogenic agents has been isolated. In the case of some of these cytopathogenic agents, etiological association with the clinical picture observed seems to have been demonstrated clearly, while in other instances the agents isolated must be investigated more extensively before etiological significance can be assigned to them.

In *The Journal of Immunology*, April, 1954, two papers appear by Franklin A. Neva and John F. Enders in which they report the isolation by means of tissue culture of cytopathogenic agents from a group of patients suffering from an unusual epidemic exanthem.[1] Another such agent, distinctly different from the other strains, was recovered about the same time from a child whose clinical manifestations were highly suggestive of roseola infantum.[2] The tissue culture methods employed included suspended cell (flask) cultures of human kidney tissue, and roller tube (implant) cultures of human embryonic skin and muscle tissue, postnatal foreskin tissue, and human uterine tissue.

The first of the two papers describes studies carried out on a group of eighteen patients seen during the late summer of 1951. In and around the Boston area at this time an epidemic exanthem occurred, for the most part in children, which was characterized clinically as a mild febrile disease of short duration, with moderate fever for one or two days, and accompanied by a skin rash appearing on the face as well as the trunk. From these eighteen patients stool specimens, throat swabs or washings, and blood specimens were obtained. No cytopathogenic agents were isolated from the throat washings or from throat swabs. From the stool specimens obtained from these patients, seven cytopathogenic agents were isolated, which gave evidence in tissue culture of being intracellular parasites, and which showed consistently definite and characteristic pathogenic effects upon the cells of the tissue cultures inoculated. All seven strains isolated seemed to be similar in the type of cytopathogenesis produced. In most instances the changes in these cultures could be distinguished readily by the observers from those produced in similar cultures by other agents, e.g., the virus of herpes simplex, or of poliomyelitis.

The cytopathogenic effect is described as occurring primarily in the fibroblasts of the tissue cultures, especially in the case of the roller-tube implants. Epithelial cells appeared to remain intact and seemed to be unaffected. Cellular degeneration progressed relatively slowly. These observations are in striking contrast to those recorded by the authors in their wide experience with the propagation of strains of poliomyelitis virus. In tissue cultures infected with strains of polio virus, degeneration progresses rather rapidly and epithelial cells, as well as fibroblasts, are destroyed.

Attempts to infect mice with these newly isolated strains were not successful. However, it is of considerable interest that from the stool specimens of two of the patients strains of Cox-

sackie virus, identified as Group A, type II, were isolated. These isolations were accomplished by means of direct inoculation of fecal suspensions into suckling mice. Attempts to isolate these Coxsackie strains in tissue culture preparations were unsuccessful.

Serum specimens during the acute and convalescent phases of the disease were available in five of the seven patients. All five showed during the course of clinical recovery an increasing titer of neutralizing antibody to one or two of the newly isolated agents, and on the basis of controlled laboratory investigations, the authors concluded that these several infectious agents, isolated directly by means of human tissue culture from patients showing the exanthematous manifestations described, are either identical immunologically, or immunologically very closely related.

A second paper by Neva and Enders[2] appearing in the same issue deals with the isolation of another cytopathogenic agent from a fecal specimen which was obtained from a patient on the eighth day of an illness very similar clinically to roseola infantum. The patient was a male child, 2 years of age, who, without any definite prodromal signs, developed a temperature of 104.4° F. The temperature was sustained, and on the third day of illness was still 102° F. On the fourth day the temperature fell to 100.2° F. At this time a rash appeared, evident first about the shoulders and thorax, then spreading down to involve the trunk. The rash lasted for a period of about three days.

A suspension prepared from the fecal specimen obtained on the eighth day of illness, yielded on tissue culture an agent which brought about striking and unusual cytopathogenic effects. The type of cellular degeneration observed, particularly in the roller-tube implant cultures, was considered by the authors to be unique in their experience, and could be distinguished from that characteristic of other cytopathogenic agents. "In fibroblasts . . . the earliest change noted was swelling of the affected cells followed by slowly progressing granular degeneration of the nuclei. The cells often became greatly enlarged and assumed bizarre shapes or forms. The peculiar granular or stippled appearance of the cell nuclei was a striking feature." In kidney tissue cultures, the cells of which are primarily epithelial in type, the degenerative changes induced by the agent concerned chiefly granulation of nuclear substance and alteration of normal cell boundaries. Excellent photomicrographs illustrating these cellular changes are included in the publication.

Serum specimens were obtained from the patient on the third day and on the twenty-eighth day following the onset of illness. Antibody studies carried out with these specimens demonstrated the development of neutralizing antibodies to the agent newly isolated. It is of interest that again the cytopathogenic agent recovered from stool failed to produce observable change when inoculated into mice, even on serial passage in suckling mice.

On the basis of these investigations it seems likely that the cytopathogenic agent isolated from the stool of a patient showing clinical features of roseola infantum has etiological significance. However, the authors stress the need for caution in associating causally a newly isolated infectious agent with the clinical manifestations observed in the patient from whom the infectious material was obtained. They re-emphasize that isolation per se of a cytopathogenic strain, particularly from stool material, does not mean necessarily that an etiological relationship with the clinical entity has been established. However, the development during the course of clinical recovery of type specific antibodies against the newly isolated agent lends considerable weight to the conclusion that the agent in question does have etiological significance. In this

connection Neva and Enders refer to the experience of Huebner and his associates with numerous strains of Coxsackie virus which "led them to emphasize the necessity for controlled epidemiologic studies before an etiologic role of a new organism can be established."

The isolation of such a cytopathogenic agent from stool material obtained from a patient showing clinical manifestations very similar to those observed in roseola infantum is of particular interest in the light of previous studies concerning the etiology of this disease.[3]

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

Vital statistics of the U. S. Department of Health show that 1,568 infant deaths were classified as due to accidental suffocation. Under one year of age 5,315 were ascribed to "asphyxia, cause not specified." There surely must be something wrong somewhere when the cause of death cannot be specified or found at autopsy. The reason for this may lie in part in the fact that the pathologist never includes the posterior nares in his examination to determine the presence of an atresia.

I am strongly of the opinion that asphyxia neonatorum with atelectasis found at autopsy may be due in part to an unrecognized bilateral atresia of the posterior nares. This relationship was described by Otto in 1829. What has happened to this work since then I do not know.

In my attempt to discover the reason for this lost information, I learned that almost all cases of suffocation are autopsied by the medical examiner. There is a law in New York State which forbids mutilation of the body before burial. One of the medical examiners told me that to remove part of the hard palate to obtain a specimen of the posterior nares is considered mutilating and therefore is not done. Frequently the exact cause of death in cases of suffocation is not found, when it could very well be due to an atresia of the posterior nares if only an investigation of this area had been established. Proof of such relationship, therefore, cannot be determined until such time as the pathologists will begin to include the posterior nares by removing a specimen en bloc in all infant suffocation deaths where no other pathology could be found to account for the infant's death.

The clinical reason for believing that suffocation is due to a bilateral atresia of the posterior nares is based upon the fact that most infants will not open the mouth to breathe if they cannot breathe through the nose. Proof of such a phenomenon can easily be determined with almost any normal newborn infant by simply pinching the nostrils together, cutting off the air through the nose, when he is resting quietly. It will be noticed that in most instances, but not necessarily in all, that in the infant's attempt at forced nasal breathing, he will close the mouth tighter, become red in the face, toss his head from side to side, and manifest signs of impending asphyxia, until the fingers are released from the nose.

Atresia of the posterior nares as a congenital pathological entity is not even mentioned in any classification on vital statistics as a cause of death under infant suffocation.

Potter and Adair, in their excellent book on *Fetal and Neonatal Death*, make no mention of atresia of the posterior nares, not because it does not exist, but because it was never considered.

I am almost certain that if more physicians were made aware of this situation, the lives of many infants up to about 5 months of age would be saved.

HENRY H. BEINFIELD, M.D.

News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at New York City, April 30, May 1 and 2, 1954.

Dr. William E. Baldock, 196 E. State St., Columbus, Ohio.

Dr. Giulio John Barbero, 36 Letitia Lane, Media, Pa.

Dr. Sidney Bennett, 196-05A 67th Ave., Fresh Meadows, L. I., N. Y.

Dr. Harold Richard Berger, 250 Elizabeth Ave, Elizabeth, N. J.

Dr. Jerome David Berman, 248 Pharr Rd., N.E., Atlanta, Ga.

Dr. Alexander Blum, Jr., 34-40 S. Bedford Rd., Mount Kisco, N. Y.

Dr. David A. Brown, 160 Post Rd., Darien, Conn.

Dr. Elizabeth Lillian Brown, 39-04 48th St., Long Island City 4, N. Y.

Dr. Arthur Eugene Burns, 860 Herrick Rd., Cleveland, Ohio.

Dr. William Felix Calhoun, Jr., 3461st ASU, U. S. Army Hospital, Camp Rucker, Ala.

Dr. Frank J. Cozzetto, 2325 Panorama Ave., Boulder, Colo.

Dr. Allen Carrol Crocker, 300 Longwood Ave., Boston 15, Mass.

Dr. Mary Ophelia Cruise, 922 Poplar Blvd., Jackson, Miss.

Dr. Estelle Rose De Vito, 301 E. 21st St., New York, N. Y.

Dr. William Rowlett Dorsey, 14 Beckford St., Salem, Mass.

Dr. James Edgar Drorbaugh, 3030 Town Line Rd., Rochester 18, N. Y.

Dr. Herbert Melvyn Eskwitt, 215 W. 88th St., New York 24, N. Y.

Dr. William J. Fanizzi, 24-20 27th St., Astoria 2, N. Y.

Dr. Louis A. Farchione, 711 E. Genesee St., Syracuse, N. Y.

Dr. John Eugene Farley, Jr., 343 Willett Ave., Riverside 15, R. I.

Dr. Anthony B. Felice, 46 Southgate Court, Brooklyn 23, N. Y.

Dr. Michael Joseph Gavenchak, 191 Yorkshire Dr., Biloxi, Miss.

Dr. Stanley B. Gittelson, 300 Cedarhurst Ave., Cedarhurst, N. Y.

Dr. H. William Goldblatt, 34 Buswell Ave., Methuen, Mass.

Dr. Pearl Reiffel Gollin, 55 E. Washington, Chicago 2, Ill.

Dr. Sylvia Preston Griffiths, 9 Howe St., New Haven, Conn.

Dr. Melvin Malcolm Grumbach, Harriet Lane Home, Johns Hopkins Hospital, Baltimore 5, Md.

Dr. A. Charles Hoffman, 219-50 Hartland Ave., Queens Village, N. Y.

Dr. Milton Henry Hollander, U. S. Army Hospital, Fort Hamilton, Brooklyn, N. Y.

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Dr. Raymond Koloski, 54 Noxon St., Poughkeepsie, N. Y.

Dr. Louis Frederick Kuehn, 106 Richmond Dr., S.E., Albuquerque, N. Mex.

Dr. Louis A. Lame, 2028 Chestnut Blvd., Cuyahoga Falls, Ohio.

Dr. Anton Nathaniel Lethin, Jr., Phys. Dept., Yale University School of Medicine, 333 Cedar St., New Haven, Conn.

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Dr. Homer Jack McDonald, 2909 Highland Ave., Birmingham, Ala.

Dr. Florence Marshall, 525 E. 68th St., New York 21, N. Y.

Dr. Marian C. Maynard, 3624 MacArthur Blvd., Oakland 19, Calif.

Dr. Robert Francis Mealy, 6 Harrison St., Taunton, Mass.

Dr. Tom Sperring Mebane, 1300 S. Allen St., State College, Pa.

Dr. Winfield Tyson Moyer, 342 Main St., Manchester, Conn.

Dr. Thomas Joseph Murphy, 145 W. Elm St., Brockton, Mass.

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Dr. Edgar Brownell Phillips, 319 Longwood Ave., Boston, Mass.
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Dr. Nathaniel Joseph Pulver, 10 Franklin Ave., White Plains, N. Y.
Dr. Harvey Oliver Randel, CSCN/CHSA No. 19, Navy No. 510, FPO New York, N. Y.
Dr. William Harry Robison, Carlton Terrace Apts., 920 S. Jefferson St., Roanoke, Va.
Dr. Arthur Allport William Roe, 648 Main St., Laconia, N. H.
Dr. Charles A. Roy, 134 Everett St., Southbridge, Mass.
Dr. Jerome H. Rusoff, 357 Ashford Ave., Dobbs Ferry, N. Y.
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Dr. Victor L. Szanton, 259 Main St., Ansonia, Conn.
Dr. Ralph Thomas Tella, 55 Glenbrook Rd., Stamford, Conn.
Dr. Charles Bunnell Terhune, 129 Summit Ave., Summit, N. J.
Dr. Howard Weiss, 6627 N. Francisco Ave., Chicago 45, Ill.
Dr. Harold Jens Wheeler, 42 Wedgemere Ave., Winchester, Mass.
Dr. Frederick G. Whoriskey, 51 Brattle St., Cambridge, Mass.
Dr. Ruth Wong, 281 E. 33rd St., Paterson, N. J.
Dr. Lydia T. Wright, 1453 Jefferson Ave., Buffalo 8, N. Y.
Dr. Hyman Zahtz, 153-02 77th Rd., Flushing 67, N. Y.

The next oral examination will be held in Chicago, Ill., Oct. 8, 9, and 10, 1954.

The following were certified in the subspecialty of Pediatric Allergy at the examination in Rochester, N. Y., on May 9, 1954.

Dr. Maclyn Cagan, Medical Tower, 31 Lincoln Park, Newark, N. J.
Dr. Cecil Collins-Williams, 1421 Danforth Ave., Toronto 6, Ontario, Canada.
Dr. Douglas Edward Johnstone, 216 Meigs St., Rochester 7, N. Y.
Dr. Herman Lubens, 11-05 Fair Lawn Ave., Fair Lawn, N. J.
Dr. Rocco J. Martoccio, 250 Genesee St., Utica, N. Y.
Dr. Arthur H. Rosenblum, 2376 E. 71st St., Chicago, Ill.
Dr. Frederic Speer, 2601 Parallel Ave., Kansas City, Kan.

Dr. A. B. Schwartz has been compiling a Cumulative Index of the Current Pediatric References, January through June, 1954, which have appeared from month to month in the JOURNAL. It will be ready by July 1 and can be obtained by addressing Pediatric References, c/o Marquette University School of Medicine, 561 N. 15th St., Milwaukee 3, Wis.

Dr. Samuel Z. Levine, professor of pediatrics at the Cornell University Medical School, was awarded the sixth annual alumni award for outstanding contributions to medicine at the annual alumni reunion of Cornell Medical College.

Dr. Hattie E. Alexander of New York has been given a citation by Goucher College for her treatment of meningitis.

At the April meetings of the Medical Board and the Board of Trustees of The Skin and Cancer Hospital of Philadelphia, Dr. Harris Perlman was appointed Chief of the Dermatological-Pediatric Service and also a member of the Medical Board.

At the sixty-fourth annual meeting of the **American Pediatric Society,** held at Buck Hill Falls, May 3 to 5, 1954, the following officers were elected for the ensuing year:

President: Dr. Alfred H. Washburn
Vice President: Dr. Amos U. Christie
Secretary-Treasurer: Dr. Aims C. McGuinness
Recorder-Editor: Dr. Stewart H. Clifford
Member of the Council: Dr. Waldo E. Nelson

The following were elected to membership:

Dr. Jay M. Arena, Durham
Dr. James B. Arey, Philadelphia
Dr. Susan C. Dees, Durham
Dr. J. Roswell Gallagher, Andover
Dr. Vincent C. Kelley, Salt Lake City
Dr. John F. McCreary, Vancouver
Dr. Edward B. D. Neuhauser, Boston
Dr. Julius B. Richmond, Syracuse
Dr. Conrad M. Riley, New York
Dr. Walter B. Seelye, Seattle
Dr. George M. Wheatley, New York
Dr. Samuel W. Wishik, Pittsburgh

The 1955 meeting of the **American Pediatric Society** will be held in Quebec in association with the **Canadian Pediatric Society** and the **British Pediatric Society.** The Society voted to hold a meeting west of the Mississippi in 1957.

At the meeting of the **Society for Pediatric Research,** which was held in Buck Hill Falls, Pa., on May 5 to 7, 1954, the following officers were elected for 1954-1955:

President: Dr. Charles Janeway
Vice President: Dr. Wolf Zuelzer
Secretary-Treasurer: Dr. Sydney Gellis
Members of the Council: Drs. Charles Kempe, Charles Lowe, John McCreary, Margaret Smith, Henry Barnett, Frederick Robbins.

The following were elected to membership in the Society:

Dr. Leonard Apt, Boston
Dr. William Bergstrom, Syracuse
Dr. Samuel Bessman, Washington
Dr. Joseph Burchenal, New York
Dr. John Craig, Boston
Dr. Robert Ely, Salt Lake City
Dr. Harry Feldman, Syracuse
Dr. Lawrence Finberg, Baltimore
Dr. Samuel Foman, Cincinnati
Dr. F. C. Fraser, Montreal
Dr. Robert Kaye, Philadelphia
Dr. Benjamin Landing, Cincinnati
Dr. Bernard Laski, Toronto
Dr. Paul Lurie, Indianapolis
Dr. Donald Pickering, San Francisco
Dr. Charles Read, Winnipeg
Dr. Nathan Smith, Los Angeles.

Book Reviews

The Allergic Child. Harry Swartz, M.D., New York, 1954, Coward-McCann, Inc., 297 pages. Price $3.95.

It is stated on the cover panel that this book was written for the layman or, as it is expressed, "the parent in the street." It is, however, far above the heads of the average parent for whom it is said to have been designed. It is rather a highly readable textbook for the physician who does not specialize in allergy who would like to have some general knowledge of this field particularly applicable to dealing with the parents of allergic children. As such it is regrettable that specific references are not given to the many fine examples of specific cases which the author uses to illuminate the points he is trying to make. It is somewhat regrettable, also, that in the acknowledgment no mention is made of Dr. Lewis Webb Hill and perhaps a few other pediatricians whose

contributions have been far more significant than a number of others mentioned by the author.

The first chapter of the book is interesting but highly philosophical and could easily have been omitted. The book contains very few significant omissions or errors. In the discussion of papular urticaria, insect bites have been mentioned as the presently accepted most common etiological factor. The discussion of psychsomatics is exceptionally well written with understanding and highly commendable restraint. The chapter on nutrition has too much detail not significantly related to the topic under consideration and would not be interesting to anyone but a physician particularly interested in this subject. The appendix contains valuable information regarding foods and environmental allergens, and also gives the American Foundation for Allergic Diseases some much needed and well-merited publicity.

Dr. Swartz has done the allergic child a real service by his continued emphasis that the policy of neglect, which is still advocated by the majority of physicians, is highly prejudical to the best interests of the child. The physician who tells a parent not to bother about his child's allergies because the child will eventually "outgrow" them not only exposes his own ignorance, but often does a very harmful disservice to his patient.

Taken altogether the book is well written and should prove interesting and helpful to the highly intelligent layman, to the physician who does not specialize in allergy, and to the allergist who is desirous of keeping up with all phases of his specialty.

J. G.

Lecciones de terapeutica infantil. Juan P. Garrahan and Collaborators, Buenos Aires, 1953, Libreria "El Ateneo," 619 pages.

This is a new edition of Prof. Garrahan's text which is extensively used and read in the Central and South American countries. As is usual in modern pediatric texts a large number of the chapters have been contributed by his colleagues in Argentina.

Colloque sur les Acides Aminés. Bâle, 1954, S. Karger, 333 pages. Price Swiss fr. 25.

The papers presented at a symposium on the amino acids held in Lausanne in April, 1953. In all, about fifty papers are presented by European scientists from many countries. The discussions include methods, physiopathologic problems, the synthesis into proteins, aminoacidemia and aminoaciduria. The section on clinical problems and therapeutics is of most interest to the practitioner. Most of the discussions are in French and a number in English and in German. Unfortunately a résumé or summary does not follow each article in the other language.

Kinderorthopädie. Rupprecht Bernbeck, Stuttgart, 1954, Georg Thieme Verlag, 234 pages. Price DM 39 ($9.30).

An excellent discussion of the orthopedic conditions of childhood by Dr. Bernbeck, Privatdozent at the University of Munich. Many of the 179 illustrations in the text are of unusual fine quality. The discussion of some conditions such as severe rachitic deformities and tuberculosis of the bones recalls the time when these conditions were common in this country. Today they are, relatively speaking, curiosities. Orthopedics in the United States has in recent years become to a large extent the specialty of traumatic surgery. It is interesting to find this monograph concerned with the derivation of the words, "the straight child."

Music Therapy. Edward Podolsky, M.D., New York, 1954, Philosophical Library, 335 pages. Price $6.00.

A collection of discussions of the use of music in therapy. In all, some forty physicians and therapists have contributed their experiences. A number of the discussions have appeared previously in journals in the field of psychiatry, and most are concerned with music as a means of controlling psychotic patients. A few discuss the use and value of music in other conditions and in the hospital and operating room.

Editor's Column

RETROLENTAL FIBROPLASIA

FOR more than a year the JOURNAL has been trying to obtain a review on retrolental fibroplasia. Those approached have shied off on the plea that so much research work is under way in this new pediatric disease that a review would probably be incomplete and out of date by the time it was published. For this reason we have commented several times editorially on what were seemingly important contributions to a knowledge of its etiology and prevention. In the April 15 issue of the *New England Journal of Medicine* Drs. Ingalls and Purshotten of Boston, in a discussion of "Oxygenation and Retrolental Fibroplasia," present an excellent review of RLF with sixty-five references. They reach the conclusion that the condition is brought on most frequently by excesses of oxygen supply to the premature infant in the neonatal period. They feel, however, that other factors such as excessive warmth and humidity, electrolyte shifts, and enzyme derangements probably influence the onset and severity of the disease.

We had hardly finished reading this discussion when in the May 15 issue of the *J.A.M.A.*, Lammon, Guy, and Dancis of New York reported on the best controlled study which has so far appeared. Premature infants, 4 pounds or under, on the Bellevue Hospital Service were alternately placed in high- and low-oxygen concentrations. All other aspects of the incubator care such as nursing and feeding were identical. Of thirty-six infants in the high-oxygen group, twenty-two (61 per cent) showed retinal vascular changes and eight (22 per cent) irreversible cicatricial RLF. Of twenty-eight in the low-oxygen group only two (7 per cent) showed vascular changes and none developed permanent changes. They believe RLF is directly related to excessive oxygen administration, and that it can be controlled by "severely limiting oxygen administration to premature infants."

At the recent May meeting of the American Pediatric Society, Rothmund, Harper, and Rider presented an epidemiologic survey of RLF in Maryland. They found the prevalence between two and three times as great as was recently found in a similar survey in New York State. In their study the various newborn hospital services were graded. It was not surprising to learn the better the service the higher the incidence of RLF.

"POLIO HYSTERIA"

WE ARE all conscious of what has aptly been termed "polio hysteria." It is easy to understand how the laity has been conditioned to fear polio through the tremendous publicity that has been given the disease by such measures as the Polio Foundation financial campaigns, the gamma globulin episode of recent medical history, and the current mass experiment in

vaccination. It is almost useless to try to point out that far more children die and are crippled each year from accidents than from polio. A child is killed in an unnecessary or preventable accident and no one seems to become excited, nor consider that their child may be next. But let one case of polio develop in a community or neighborhood and a panic often follows. So long as the disease continues to be relatively overemphasized by lay publicity there is little we can do about it.

What we should be concerned about is a kind of extension of this "polio hysteria" to physicians when the polio season comes round. A tentative diagnosis of polio is made in many conditions in which polio would not have been considered at a different time of year. Only a little more careful study of the patient was needed before the polio "tag" could be eliminated. Two years ago the JOURNAL published a study from the Philadelphia Hospital for Contagious Diseases* in which it was found that in a ten-year period 1,420 patients had been admitted to the hospital with the diagnosis of poliomyelitis. In 409 (28.9 per cent) the diagnosis was revised after clinical and laboratory evaluation. Other services have reported a similar situation. To enumerate the diseases and conditions that have been erroneously diagnosed as polio during the "season" would take at least two pages in fine type. In this issue (page 51) a small group of neuromuscular diseases is described by Moskowitz which emphasizes the point we are making. We are quite willing to grant that not infrequently the differential diagnosis may be difficult—but not to the extent of a 30 per cent inaccuracy. This, to our mind, reflects poor case study and an extension of "polio hysteria" to the physician.

*Dawson, LaBoccetta, Tornay, and Silverstein: J. PEDIAT. **40**: 71, 1952.

PERTUSSIS VACCINE

THE change that was made in indicating the potency of pertussis vaccines a number of months ago has puzzled many practitioners. In this issue (page 57) Dr. Margaret Pittman describes the painstaking studies of pertussis vaccines over many years which led the National Institutes of Health to change the labeling requirement from millions of bacteria to a unit of potency. Under the Biological Control Law, the National Institutes of Health has the responsibility of formulating requirements and regulations which producers of commercial vaccines must meet.